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(71) Applicants *(for all designated States except US)*: NEUROGEN CORPORATION [US/US]; 35 Northeast Industrial Road, Branford, CT 06405 (US). PFIZER, INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HORVATH, Raymond, F. [US/US]; 973 Little Meadow, Guilford, CT 06437 (US). TRAN, Jennifer [US/US]; 56 Barier Hill Drive, Guilford, CT 06437 (US). DE LOMBAERT, Stephane [US/US]; 37 Concord Drive, Madison, CT 06443 (US). HODGETTS, Kevin, Julian [US/US]; 224 Reservoir Road, Killingworth, CT 06443 (US). CARPINO, Philip, A. [US/US]; 50 Meridian Street, Groton, CT 06340 (US). GRIFFITH, David, A. [US/US]; 10 Barley Hill Road, Old Saybrook, CT 06475 (US).

(74) Agents: RICHARDS, John; Ladas & Parry, 26 West 61st Sreet, New York, NY 10023 et al. (US).

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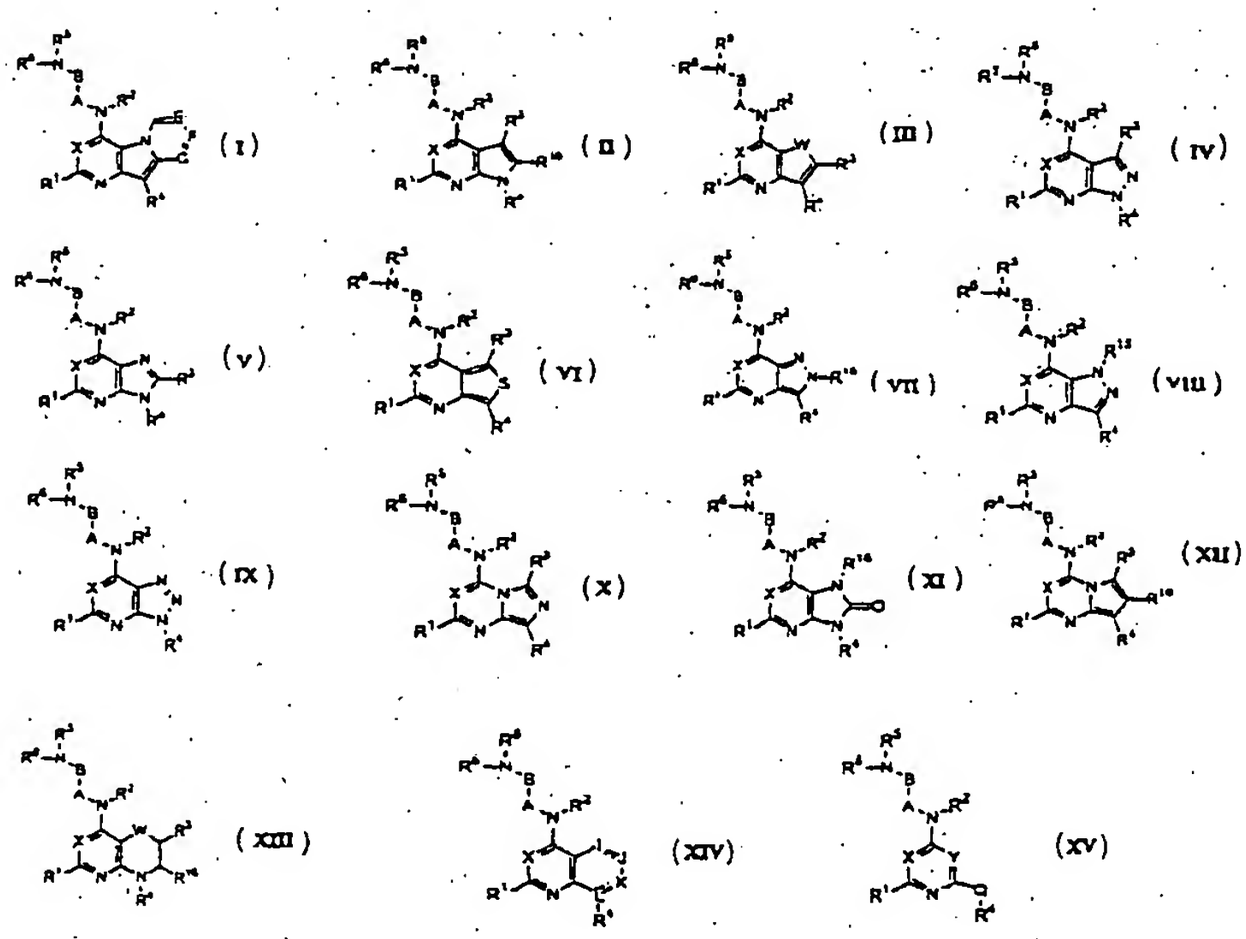
(54) Title: CERTAIN ALKYLENE DIAMINE-SUBSTITUTED HETEROCYCLES



(57) Abstract: The present invention also provides a general method to whereby mono-, bi-, or tri-cyclic heterocycles may be modified to obtain potent antagonists at the NPY_1 receptor. The present invention provides novel, potent, non-peptidic antagonists of NPY receptors, particularly, the NPY_1 receptors, designed from a selection of mono-, bi-, or tri-cyclic heterocyclic cores. This invention relates to novel compounds, compositions, and methods for the treatment of physiological disorders associated with an excess of neuropeptide Y. The novel compounds encompassed by the present invention are those of formula (I)-(XV), wherein X is N or CR^{14}; W is S, O, or NR^{15}; Y is N or CR^3; E, F, and G are each, independently; CR^3 or N; I and J are each, independently, C=O, S, O, CR^3R^{16} or NR^{15} when single bonded to both adjacent ring atoms, or N, or CR^3 when double bonded to an adjacent ring atom; K is N or CR^3 when double bonded to L or J, or O, S, C=O, CR^3R^{16}, or NR^{15} when single bonded to both adjacent ring atoms, or N or CR^3 when double bonded to an adjacent ring atom; L is N or CR^{16} when single bonded to all atoms to which it is attached, or C (carbon) when double bonded to K; the 6- or 7-membered ring that contains I, J, K, and L may contain from 1 to 3 double bonds, from 0 to 2 heteroatoms, and from 0 to 2 C=O groups, wherein the carbon atom of such groups are part of the ring and the oxygen atom is a substituent on the ring; Q is O or NR^{15}. Such compounds inhibit the activity of neuropeptide Y at those receptors are useful in treating physiological disorders associated with an excess of neuropeptide Y, including eating disorders, such as, for example, obesity and bulimia, and certain cardiovascular diseases, for example, hypertension.

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APPLICATION FOR UNITED STATES LETTERS PATENT IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

(Case No. U-012958-7)

(FROM PROVISIONAL U012426-2)

Title: Certain Alkylene Diamine-Substituted Heterocycles

SDOCID: <WO___0123389A2_I_>

Certain Alkylene Diamine-Substituted Heterocycles

Cross Reference to Related Application

This application claims priority from Provisional Application 60/156870 filed on September 30, 1999 which is incorporated herein by reference.

Field of the Invention

This invention relates to certain alkylene diamine-substituted heterocycles which selectively and potently bind mammalian neuropeptide Y (NPY) receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating physiological disorders associated with an excess of neuropeptide Y, especially feeding disorders, some psychiatric disorders, and certain cardiovascular diseases.

Background of the Invention

Neuropeptide Y (NPY) is a 36 amino acid peptide first isolated in 1982 and subsequently found to be largely conserved across species. It belongs to a large family of peptides that includes, among others, peptide YY (PYY) and pancreatic peptide (PP). NPY is believed to be the most abundant peptide in the mammalian brain. It is also found in sympathetic neurons, and NPY-containing fibers have been found in peripheral tissues, such as around the arteries in the heart, the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Central injection of NPY elicits a multitude of physiological responses, such as stimulation of feeding, increase in fat storage, elevation of blood sugar and insulin, anxiolytic behaviors, reduction in locomotor activity, hormone release, increase in blood pressure, reduction in body temperature, and catalepsy. In the cardiovascular system, NPY is believed to be involved in the regulation of coronary tone, while in the gastrointestinal tract, PYY is reported to cause inhibition of gastric acid secretion, pancreatic exocrine secretion, and gastrointestinal motility. These effects appear to be selectively mediated by various NPY receptors which currently include the Y_1, Y_2, Y_3, Y_4, Y_5, and Y_6 subtypes, in addition to the hypothetical $Y_{1\text{-like}}$ subtype. Selective peptidic agonists and antagonists have been identified for most of the subtypes, but few selective non-peptidic antagonists have been reported. The

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Y_1 and Y_5 receptor subtypes appear to be involved in appetite regulation, but their relative contribution to the modulation of food intake and energy expenditure remains unclear. The discovery of non-peptidic antagonists of the Y_1 and/or Y_5 receptor provides novel therapeutic agents, that are less prone to the shortcomings of the peptide antagonists, namely, for example, poor metabolic stability, low oral bioavailability, and poor brain permeability, for the treatment of obesity and cardiovascular disease.

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Summary of the Invention

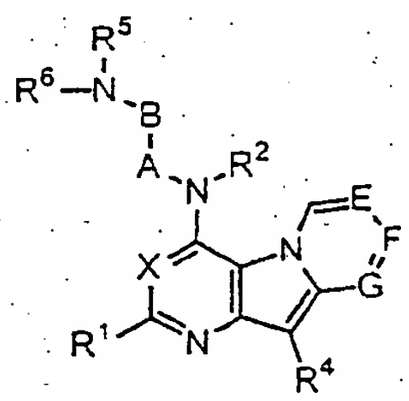
The present invention also provides a general method to whereby mono-, bi-, or tricyclic heterocycles may be modified to obtain potent antagonists at the NPY_1 receptor.

The present invention provides novel, potent, non-peptidic antagonists of NPY receptors, particularly, the NPY_1 receptors, designed from a selection of mono- , bi-, or tricyclic heterocyclic cores.

The heterocyclic cores encompassed by the compounds of formula II-XV (shown below) have been previously described. The modifications made to these heterocyclic cores to obtain potent and selective NPY_1 antagonists are entirely novel.

Compounds that interact with the Y_1 receptor and inhibit the activity of neuropeptide Y at those receptors are useful in treating physiological disorders associated with an excess of neuropeptide Y, including eating disorders, such as, for example, obesity and bulimia, and certain cardiovascular diseases, for example, hypertension.

This invention relates to novel compounds, compositions, and methods for the treatment of physiological disorders associated with an excess of neuropeptide Y. The novel compounds encompassed by the present invention are those of the formula I-XV.



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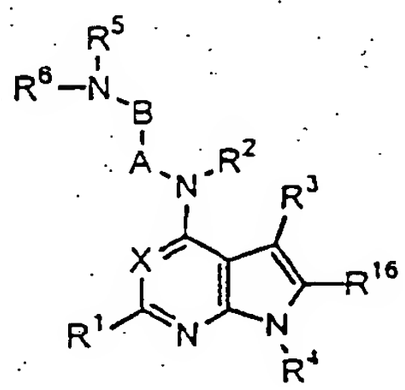

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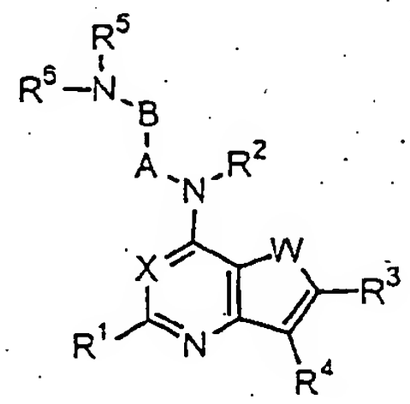

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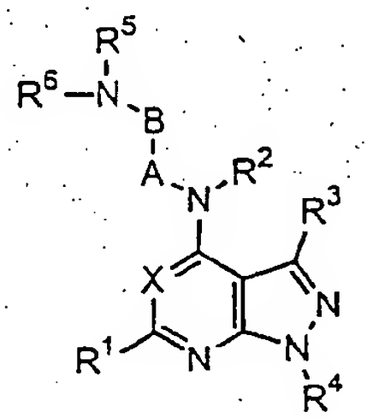

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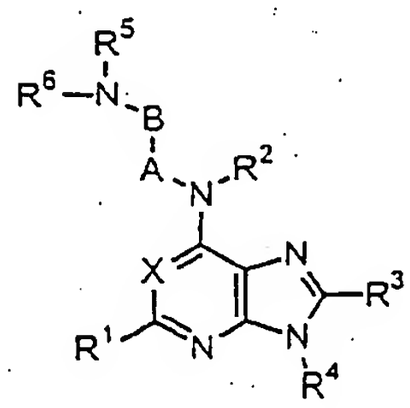

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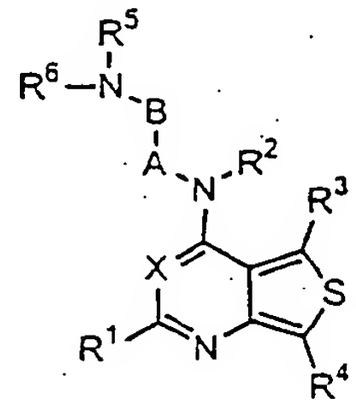

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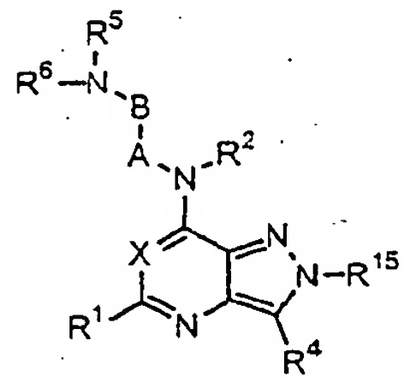

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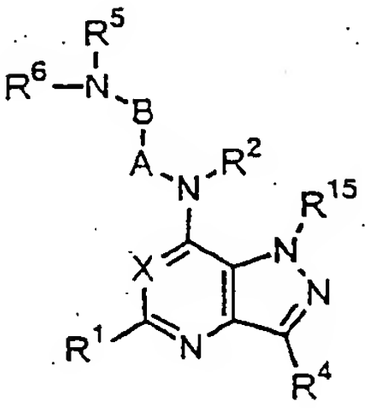

VIII

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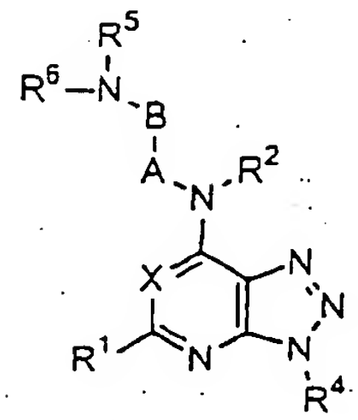

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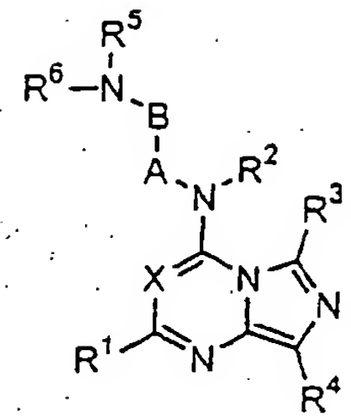

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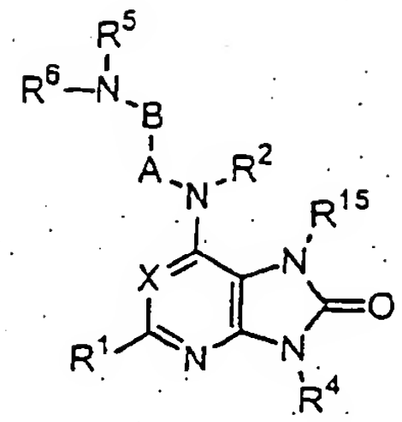

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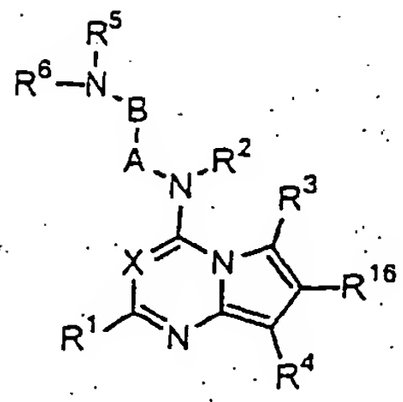

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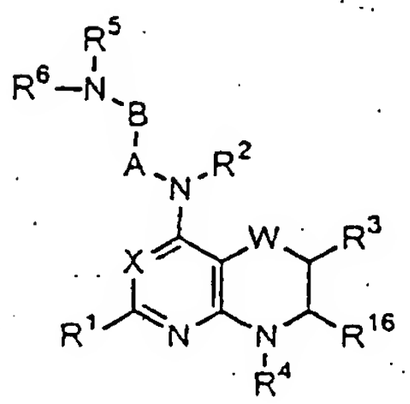

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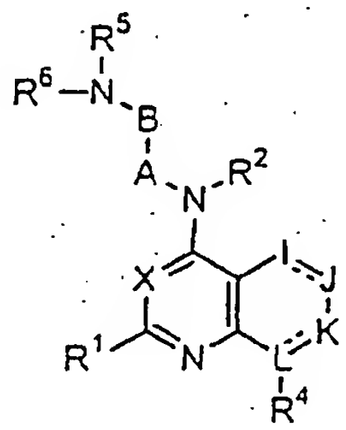

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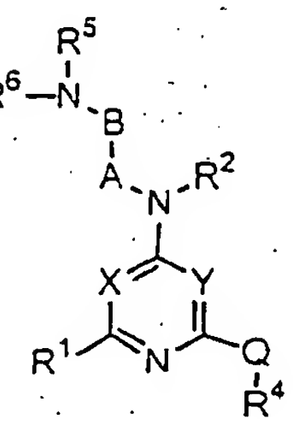

XV

wherein

X is N or CR^{14};

W is S, O, or NR^{15};

Y is N or CR^3;

E, F, and G are each, independently, CR^3 or N;

I and J are each, independently,

C=O, S, O, CR^3R^{16} or NR^{15} when single bonded to both adjacent ring atoms, or

N, or CR^3 when double bonded to an adjacent ring atom;

K is

N or CR^3 when double bonded to L or J, or

O, S, C=O, CR^3R^{16}, or NR^{15} when single bonded to both adjacent ring atoms, or

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N or CR^3 when double bonded to an adjacent ring atom;

L is

N or CR^{16} when single bonded to all atoms to which it is attached, or

C (carbon) when double bonded to K;

The 6- or 7-membered ring that contains I, J, K, and L may contain from 1 to 3 double bonds, from 0 to 2 heteroatoms, and from 0 to 2 C=O groups, wherein the carbon atom of such groups are part of the ring and the oxygen atom is a substituent on the ring;

Q is O or NR^{15};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each optionally substituted at each occurrence with R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

or R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted at each occurrence with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9,

or A and B jointly form a C_3-C_6 carbocycle, optionally substituted at each occurrence with R^7

or, as mentioned above, A and R^2 jointly form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle optionally substituted at each occurrence with R^7;

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B is $(CH_2)_n$ where n is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9,
or, as mentioned above, B and A jointly form a C_3-C_6 carbocycle, optionally substituted at each occurrence with R^7
or, as mentioned above, B and R^2 jointly form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle optionally substituted at each occurrence with R^7;

R^3 and R^{16} are selected independently at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the heterocyclic core is substituted;

R^5 is selected from:

C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C_1-C_2 haloalkyl, OR^7, cyano, NR^8R^9, $CONR^8R^9$, $COOR^7$, $SO_2NR^8R^9$, SO_2R^7, $NR^{11}COR^{12}$, $NR^{11}SO_2R^7$;

C_1-C_6 arylalkyl, C_1-C_6 heteroarylalkyl, C_5-C_8 arylcycloalkyl, or C_5-C_8 heteroarylcycloalkyl, where aryl is phenyl or naphthyl, and heteroaryl is 2-,3-, or 4-pyridyl, 2-, 4- or 5-

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pyrimidinyl, triazinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, isoxazolyl, indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyrazinyl, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothienyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, each of which is optionally with 1 to 6 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, OR^7, NR^8R^9, with the proviso that when two OR^7 or NR^8R^9 substituents are geminally located on the same carbon R^7 is not H and they can form together a C_2-C_4 ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, oxo, hydroximino, C_1-C_6 alkoximino, $SO_2NR^8R^9$, SO_2R^7, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-

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oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,1-dioxo) tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl, quinuclidinyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R^7, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$;

R^6 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_1-C_6 arylalkyl, C_1-C_6 heteroarylalkyl where aryl or heteroaryl are optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7,

or R^6 and R^2, as mentioned above, jointly form, with the 2 nitrogen atoms to which they are bound, a C_2-C_5 aminoheterocycle optionally substituted at each occurrence with R^7;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,

or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6

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heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that for $SO_2NR^8R^9$, SO_2R^{13}, R^{13} cannot be H;

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN;

R^{15} is selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 alkyl-OR^7, C_2-C_6 cyanoalkyl, C_2-C_6 alkyl-NR^8R^9;

or a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

Preferred compounds of the present invention are those where X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl. Additional prefered compounds are those wherein R^6 is phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a

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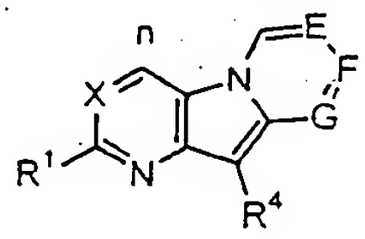
heterocycle. Other preferred compounds are those wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

This invention also encompasses, in additional embodiments, the novel compounds of formula I-XV, and the salts and solvates thereof, as well as pharmaceutical formulations comprising a compound of formula I-XV, or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, excipients, or diluents thereof.

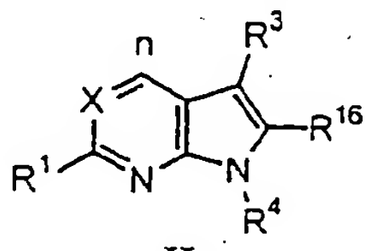
This invention also encompasses methods to treat physiological disorders associated with an excess of neuropeptide Y, such as eating and cardiovascular disorders, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of the formula I-XV.

This invention also encompasses methods of selectively inhibiting binding of NPY_1 receptors, which comprises contacting a compound of formula I-XV with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to inhibit binding of NPY_1 receptors in vitro.

As such, the present invention also provides a method to convert heterocyclic cores of formula Ia to XVa where X, E, F, G, W, I, J, K, L, Q, R^1, R^3, R^4, R^{15} and R^{16} are defined above, into compounds that potently and selectively interact with NPY_1 receptors by substituting the n-position of heterocycles of formula Ia - XVIa with a diamine group of formula $N[R^2]$-A-B-$N[R^6]$-R^5 where R^2, A, B, R^6, and R^5 are defined above.



Ia



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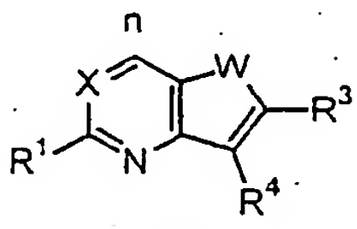

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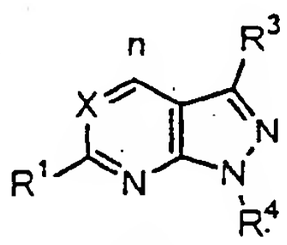

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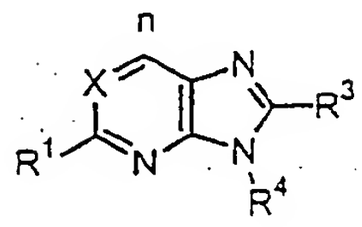
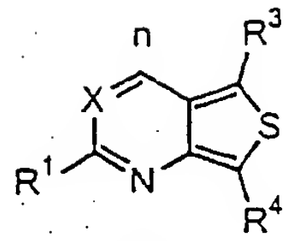


Va



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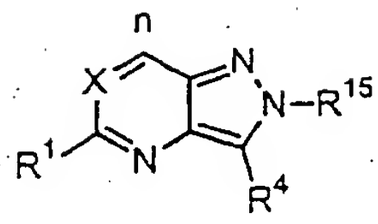

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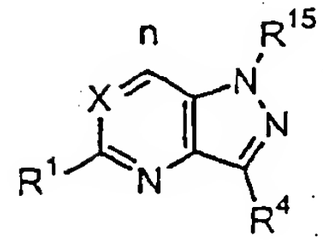

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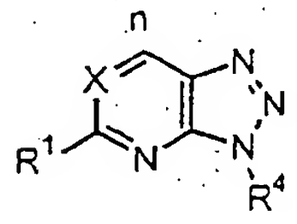

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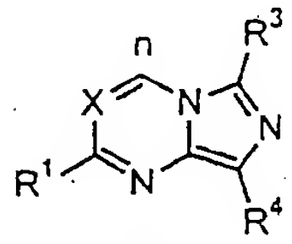

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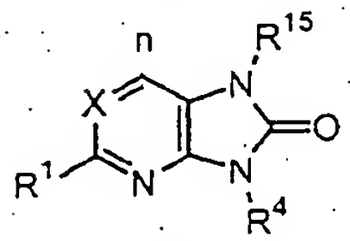

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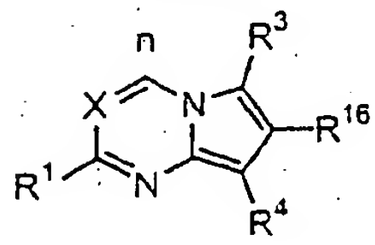

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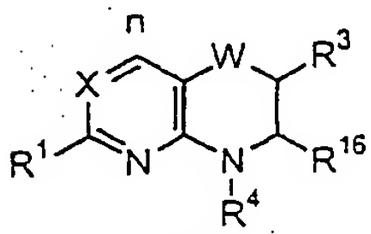
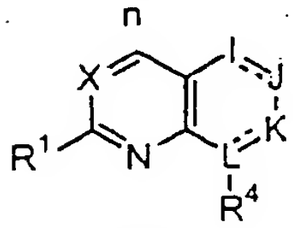
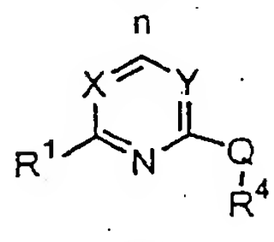


XIIIa



XIVa



XVa

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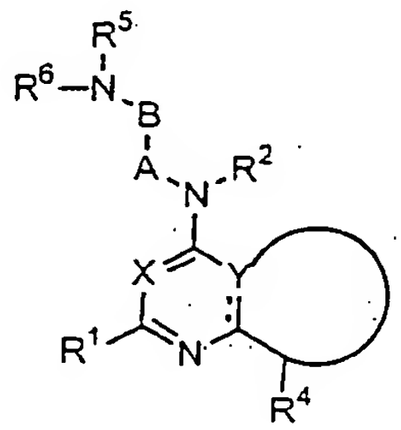
Detailed Description of the Invention

This invention relates to certain alkylene diamine-substituted heterocycles which selectively and potently bind mammalian neuropeptide Y (NPY) receptors., those of formula I-XV, which are novel and useful neuropeptide Y receptor antagonists.

In the present description, the compounds of formula I-XV may be generically described under formula A, where R^1, R^2, R^4, R^5, R^6, X, Y, A, and B are defined above.



A

In certain situations, the compounds of formula I-XV may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention, which are encompassed by formula I-XV, include, but are not limited to the compounds in Examples 1-56 and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-(CH_2)n-COOH

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where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of formula I-XV. "Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula I-XV in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of the invention are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of formula I-XV; and the like. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by formula I-XV.

Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers. The invention includes all tautomeric forms of a compound.

By "heteroatom" in the present invention is meant oxygen or sulfur, or a nitrogen atom optionally substituted by C_1-C_6 lower alkyl, C_1-C_6 arylalkyl, C_1-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_8 alkanoyl, C_1-C_6 sulfonyl.

By "alkyl", "lower alkyl", or "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "cycloalkyl", or "C_3-C_{10} cycloalkyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi-, or polycyclic ring system, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

By "(cycloalkyl)alkyl", "lower (cycloalkyl)alkyl", or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl in the present invention is meant a straight or branched alkyl substituent formed of 1 to 6

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carbon atoms attached to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, and the like.

The term "C_2-C_6 alkenyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon double bonds which may occur in any stable point along the chain, such as, for example, ethenyl, allyl, isopropenyl, and the like.

By "cycloalkenyl" or "C_3-C_{10} cycloalkenyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi, or polycyclic ring system having 3-10 carbon atoms and containing one or more carbon-carbon double bonds which may occur in any stable point in the ring, such as, for example, cyclopentenyl, cyclohexenyl, or cycloheptenyl.

The term "C_2-C_6 alkynyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon triple bonds which may occur in any stable point along the chain, such as, for example, ethynyl, propargyl, and the like.

The term "aryl" in the present invention means a monocyclic or bicyclic aromatic group having preferably 6 to 10 carbon atoms, such as, for example, phenyl or naphthyl.

The term "heteroaryl" in the present invention means an aryl group in which one or more of the ring(s) carbon atoms have been replaced with a heteroatom. Such groups preferably have 4 to 10 carbon atoms and 1 to 4 heteroatoms, such as, for example, pyridyl, pyrimidinyl, triazinyl, imidazolyl, oxazolyl, isoxazolyl, indolyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, thiazolyl, benzothiadiazolyl, triazolyl, triazinyl, pyrazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, tetrazolyl.

The term "heterocyclyl", "heterocycle" or "heterocycloalkyl" in the present invention means a saturated or partially saturated heteroaryl group.

By "C_1-C_6 arylalkyl" or "C_1-C_6 heteroarylalkyl" in the present invention is meant a branched or straight-chain alkyl group having 1-6 carbon atoms and substituted on one of the carbon atoms by an optionally substituted aryl or heteroaryl ring, such as, for example, benzyl, phenethyl, methylpyridyl, ethylpyridyl, and the like.

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By "C_5-C_8 arylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms and fused to an aryl group, such as, for example, 1,2,3,4 tetrahydronaphthalenyl, 2,3-dihydrobenzothienyl, or 2,3-dihydobenzofuranyl.

By "C_5-C_8 heteroarylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms fused to a heteroaryl group, such as, for example, 1,2,3,4 tetrahydroquinolyl, 2,3-dihydrobenzothienyl, 2,3-dihydobenzofuranyl, or indolinyl.

By "alkoxy", "C_1-C_6 alkoxy", or "C_1-C_6 alkyloxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By "cycloalkoxy", "C_3-C_{10} cycloalkoxy", or "C_3-C_{10} cycloalkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, or cycloheptoxy.

By "(cycloalkyl)alkyloxy", "(C_3-C_{10} cycloalkyl) C_1-C_6 alkoxy", or "(C_3-C_{10} cycloalkyl) C_1-C_6 alkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a 1-6 carbon chain linked to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cycloheptylmethyloxy, and the like.

By "C_3-C_6 aminocarbocycle" is meant a cyclic amino group formed by a nitrogen contained in a ring having 3 to 6 carbon atoms, such as, for example, azetidino, pyrrolidino, piperidino, perhydroazepino.

By "C_2-C_5 aminoheterocycle" is meant a cyclic amino group formed by a nitrogen contained in a ring having 2 to 5 carbon atoms and one other heteroatom, such as, for example, morpholino, thiomorpholino, piperazino.

By the terms "halo" or "halogen" in the present invention is meant fluoro, chloro, bromo, and iodo.

"Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms substituted with 1 or more halogens.

The term "C_2-C_8 alkanoyl" means an acyl group with 2 to 8 carbon atoms in a linear, branched, or C_3-C_{10} cycloalkyl arrangement, optionally substituted with 1 to 5 substituents

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independently selected at each occurrence from halogen, trifluoromethyl, OR^7, NR^8R^9, $CONR^8R^9$, $COOR^7$, or CN.

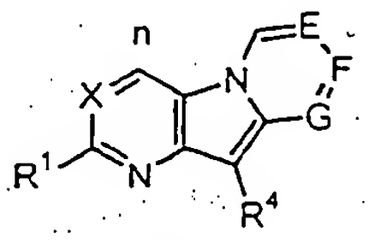
The term "C_1-C_6 alkyl sulfonyl" means an alkylsulfonyl group containing 1 to 6 carbon atoms in a linear, branched, or C_3-C_7 cycloalkyl arrangement.

The term "substituted" means that one or more hydrogen on the designated atom is replaced by the specified group, provided that the valence on the designated atom is not exceeded, and that a chemically stable compound results from the substitution.

A stable compound is defined herein as one that can be isolated, characterized, and tested for biological activity.

The term "oxo" (i.e. =O) indicates that two geminal hydrogen atoms are replaced by a double-bond oxygen group.

By "heterocyclic core" in the present invention is meant one of the following structures of formula Ia to XVa, where X, E, F, G, W, I, J, K, L, Q, R^1, R^3, R^4, R^{15} and R^{16} are defined above.



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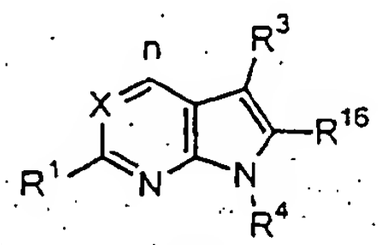

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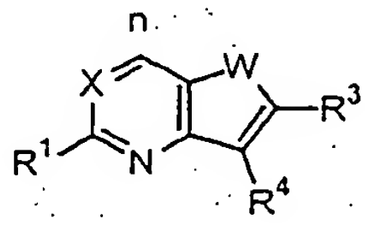

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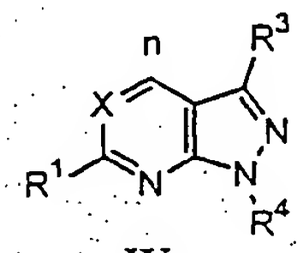

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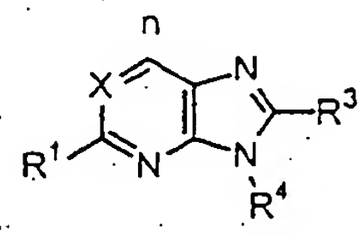

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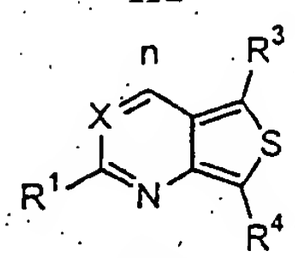

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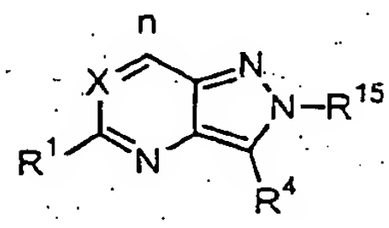
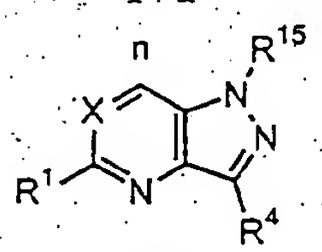


VIIa



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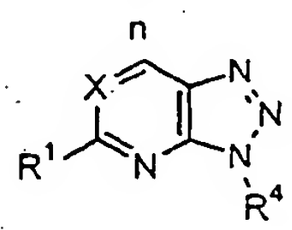

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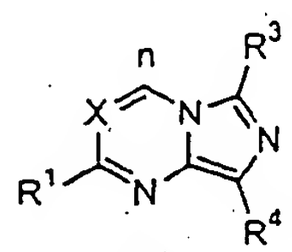

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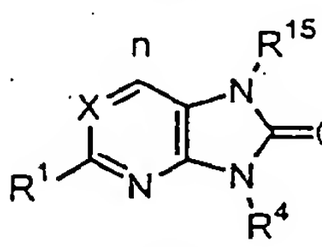

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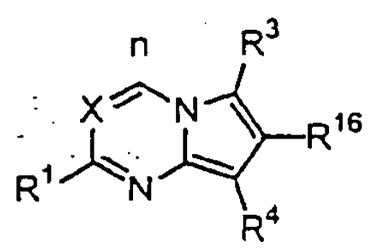

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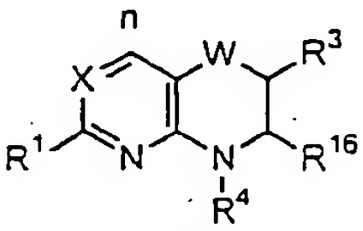

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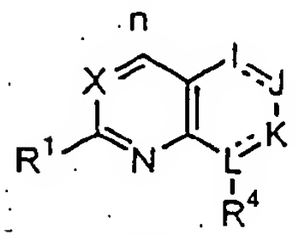
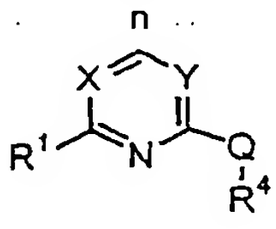


XIVa



XVa

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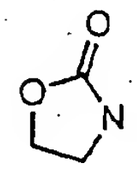
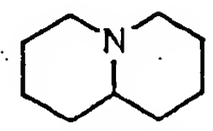
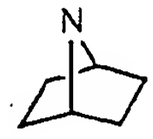
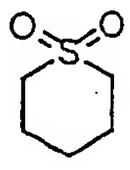
In the present invention, some of the groups specifically mentioned above are defined as follows :

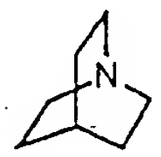
2-one-1,3-oxazolidinyl is 

1-aza-bicyclo[4.4.0]decyl is 

8-azabicyclo[3.2.1]octanyl is 

(1,1-dioxo) tetrahydrothiopyranyl is 

norbornyl is 

quinuclidinyl is 

Unless specified, the point of attachment may occur in any stable point along the above-mentioned rings.

In the present invention, the term "potent" in the context of NPY1 receptor antagonists qualifies a binding affinity with a Ki of less than 10 micromolar, preferably less than 1 micromolar, and more preferably less than 100 nanomolar in the human NPY1 binding assay.

In the present invention, the term "selective" in the context of NPY1 receptor antagonists qualifies a binding affinity with a Ki in the human NPY_1 binding assay that is 10-fold, preferably 100-fold, and more preferably 1000-fold, less than the Ki of the same compound measured in another receptor binding assay, in particular the NPY_5 and CRF_1 receptor binding assays. Binding assays for the NPY_5 and CRF_1 receptors have been described, for example, in *J. Clin. Invest.*, 102, 2136 (1998) and in *Endocrinology* 116, 1653 (1985), respectively.

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As the compounds of formula I-XV are antagonists of the Y1 receptor, they are of value in the treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of neuropeptide Y. Thus, the invention provides methods for the treatment or prevention of a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of formula I-XV or a pharmaceutically acceptable salt, solvate or prodrug thereof. The term "physiological disorder associated with an excess of neuropeptide Y" encompasses those disorders associated with an inappropriate stimulation of neuropeptide Y receptors, regardless of the actual amount of neuropeptide Y present locally. These physiological disorders may include: disorders or diseases pertaining to the heart, blood vessels or the renal system, such as vasospasm, heart failure, shock, cardiac hypertrophy increased blood pressure, angina, myocardial infarction, sudden cardiac death, arrhythmia, peripheral vascular disease, and abnormal renal conditions such as impaired flow of fluid, abnormal mass transport, or renal failure; conditions related to increased sympathetic nerve activity for example, during or after coronary artery surgery, and operations and surgery in the gastrointestinal tract; cerebral diseases and diseases related to the central nervous system, such as cerebral infarction, neurodegeneration, epilepsy, stroke, and conditions related to stroke, cerebral vasospasm and hemorrhage, depression, anxiety, schizophrenia, and dementia; conditions related to pain or nociception; diseases related to abnormal gastrointestinal motility and secretion, such as different forms of ileus, urinary incontinence, and Crohn's disease; abnormal drink and food intake disorders, such as obesity, anorexia, bulimia, and metabolic disorders; diseases related to sexual dysfunction and reproductive disorders; conditions or disorders associated with inflammation; respiratory diseases, such as asthma and conditions related to asthma and bronchoconstriction; and diseases related to abnormal hormone release, such as leutinizing hormone, growth hormone, insulin, and prolactin. See U.S. Patent 5,504,094.

Pharmaceutical Preparations

The compounds of general Formula I-XV may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular,

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intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I-XV and a pharmaceutically acceptable carrier. One or more compounds of general Formula I-XV may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I-XV may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene

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stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachid oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachid oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be

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formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I-XV may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I-XV may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 50 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 3 g per patient per day), although in some circumstances higher amoounts, fo example upto 140 mg/kg/day may be appropriate. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most eating disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of stress and depression a dosage regimen of 1 or 2 times daily is particularly preferred.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of

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administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (*Journal of Chromatography B* 1996, *677*, 1-27).

Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (*Drug Metabolism and Disposition* 1998, *26*, 1120-1127).

As discussed above, preferred compounds of the invention exhibit good activity in standard *in vitro* NPY receptor binding assays, specifically the assay as specified in Example 261, which follows. References herein to "standard *in vitro* receptor binding assay" are intended to refer to that protocol as defined in Example 261 which follows. Generally preferred compounds of the invention exhibit a K_i of about 1 micromolar or less, still more preferably and K_i of about 100 nanomolar or less even more preferably an K_i of about 10 nanomolar or less or even 1 nanomolar or less in such a defined standard *in vitro* NPY receptor binding assay as exemplified by Example 261which follows.

In appropriate case, the compounds of the invention may be employed in combination with other active agents. The invention therefore also provides pharmaceutical combination

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compositions comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound as described above a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent. To this end therefore the invention also provides a kit comprising: (a) first compound, said first compound being a compound as described above, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

Preparation of Alkylene Diamine-Substituted Heterocycles of Formula I-XV

The preparation of these heterocyclic cores, identified in formula II-XV, can be carried out according to the methods described in the following references and those cited therein:

Formula II : WO 9413676, WO 9534563, WO 9845295, EP 729758, *J. Med. Chem.*, 40(11), 1749-1754 (1997), *Bioorg. Med. Chem. Lett.*, 9(7), 967-972 (1999), *J. Med. Chem.*, 42(5), 819-832 (1999) ; *J. Med. Chem.* 42(5), 833-848 (1999);

Formula III: WO 9635689, WO 9729110, WO 9808847, WO 9847903, WO 9940091, US 5664057;

Formula IV : WO 9413677, WO 9534563, EP 0729758;

Formula V: WO 9533750, *J. Med. Chem.* 42(5), 833-848 (1999); *Bioorg. Med. Chem. Lett.*, 9(7), 967-972 (1999);

Formula VI : WO 9808847, WO 9829397;

Formula VII: EP 239191, US 5273608;

Formula VIII: US 5273608;

Formula IX: WO 9510506, WO 9735539, WO 9808847, WO 9842706, *J. Med. Chem.* 42(5), 833-848 (1999);

Formula X : WO 9808847, WO 9835967;

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Formula XI : WO 9535750, *Bioorg. Med. Chem. Lett.*, 9(7), 967-972 (1999);

Formula XII : WO 9808847, WO 9835967;

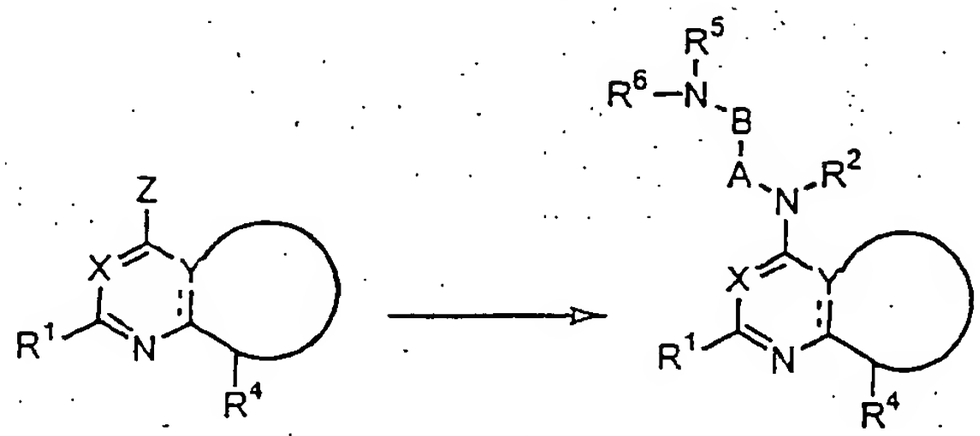
Formula XIII : WO 9744038;

Formula XIV : WO 9808846; WO 9829397, WO 9835967, WO 9847874, WO 9912908;

Formula XV : WO 9510506, WO 9533750, WO 9714684, WO 9735580, WO 9842699, EP 778277, *J. Med. Chem.* 39(22), 4358-4360 (1996), *J. Med. Chem.* 42(5), 805-818 (1999), *J. Med. Chem.* 42(5), 833-848 (1999);

An illustration of preparation methods of compounds of the present invention is given in the Schemes below. In particular displacement of a leaving group Z, as in formula 10 (scheme 1) by the appropriate substituted amine or appropriate substitution of an heterocyclic amino group, as in formula 21 (scheme 7), provides general methods to convert the heterocyclic cores of the present invention into compounds that potently interact with the NPY_1 receptor. Such transformations may require several consecutive chemical steps. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention. The disclosures of all articles and references mentioned in this application, including patents, are incorporated herein by reference.

SCHEME 1



10 A

As illustrated in scheme 1, compounds of formula A can be prepared from intermediate compounds of formula 10, where Z is halogen (preferably chloro or bromo), alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy, and where R^1, R^2, R^4, R^5, R^6, X, Y, A, and B are defined above, using the procedures outlined below.

Compounds of formula 10 react with an amine of formula H_2N-A-B-N[R^6]-R^5, where A,B, R^5 and R^6 are defined as above, in the presence or absence of a base in the presence or

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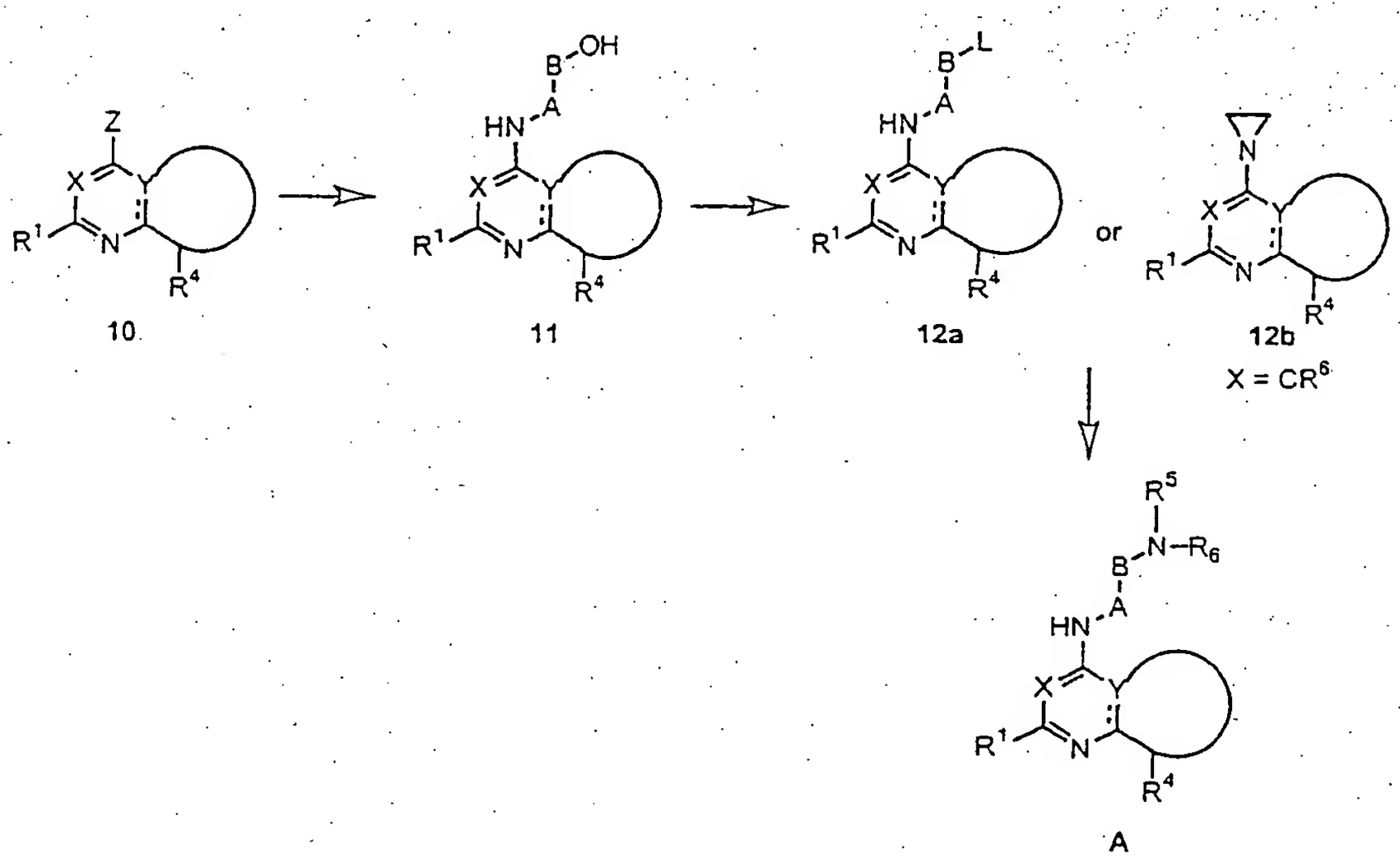
absence of an inert solvent at reaction temperatures ranging from -78°C to 250C° to generate compounds of formula A. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably CH_2Cl_2). Preferred reaction temperatures range from 0°C to 140°C.

SCHEME 2



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Alternatively, as illustrate in scheme 2, compounds of formula A can be obtained by first reacting a compound of formula **10** with an amino alcohol of formula H_2N-A-B-OH, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C to generate intermediates of formula 11. Reacting a compound of formula 11 with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from –78°C to 250°C to afford products of formula **12a** (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy) or **12b** when A and B are both CH_2 and X is CR^{14}. Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, PBr_5., CCl_4/PPh_3. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably CH_2Cl_2). Preferred reaction temperatures range from –20°C to 100°C. Compounds of formula **12a** or **12b** can then be reacted with an amine of formula $HN[R^6]$-R^5, where R^5 and R^6 are defined as above, to give a compound of formula A Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines

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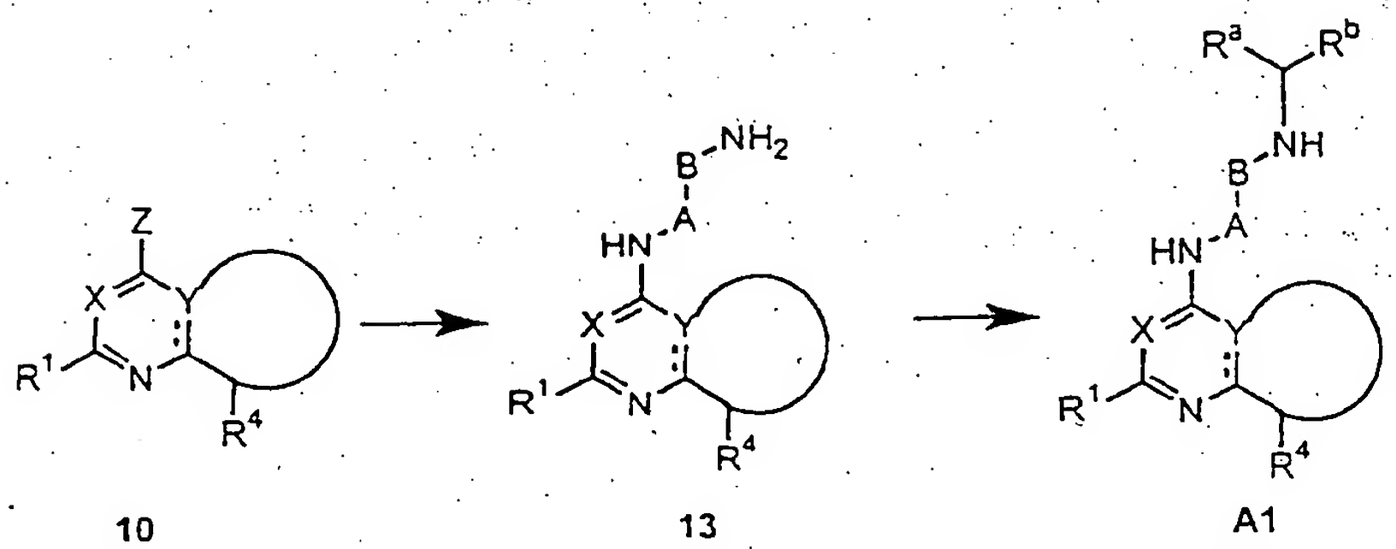
(preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably CH_2Cl_2). Preferred reaction temperatures range from 0C°C to 140°C.

SCHEME 3



10 13 A1

A subset of compounds of formula A, described under formula A1 (scheme 3), can be obtained by first reacting a compound of formula 10 with a diamine of formula H_2N-A-B-NH_2, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C to generate intermediates of formula 13. Reaction of a compound of formula 13 with a ketone of Formula R^a-C=O-R^b in the presence of a reducing agent provides a compound of

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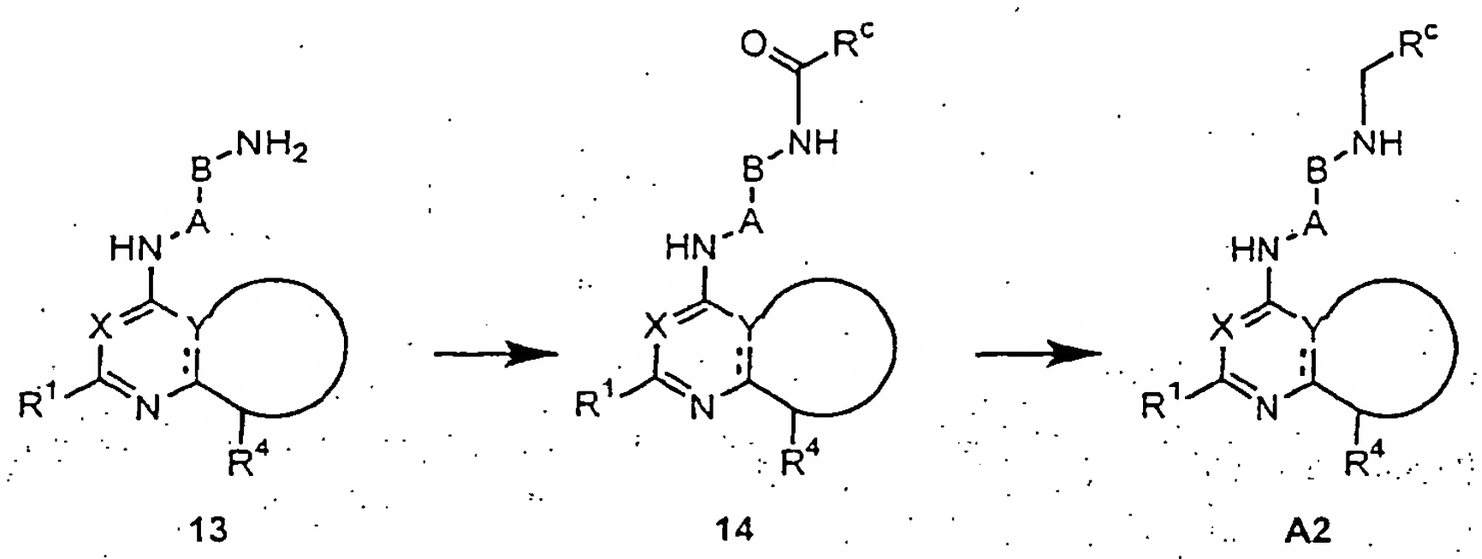
formula A1, where the grouping R^a-CH-R^b corresponds to R^3 in formula A, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -78°C to 100°C.

SCHEME 4



Alternatively, a subset of compounds of formula A, described under formula A2 (scheme 4), can be obtained by first reacting a compound of formula 13 with an activated acid of formula R^c-C=O-Z, where Z is halo (preferably chloro), O-acyl (preferably O-C=O-R^c), in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C to generate an amide intermediate of formula 14. Reaction of a compound of formula 14 with a reducing agent provides a compound of formula A2, where the grouping R^c-CH_2 corresponds to R^5 in formula A, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride),

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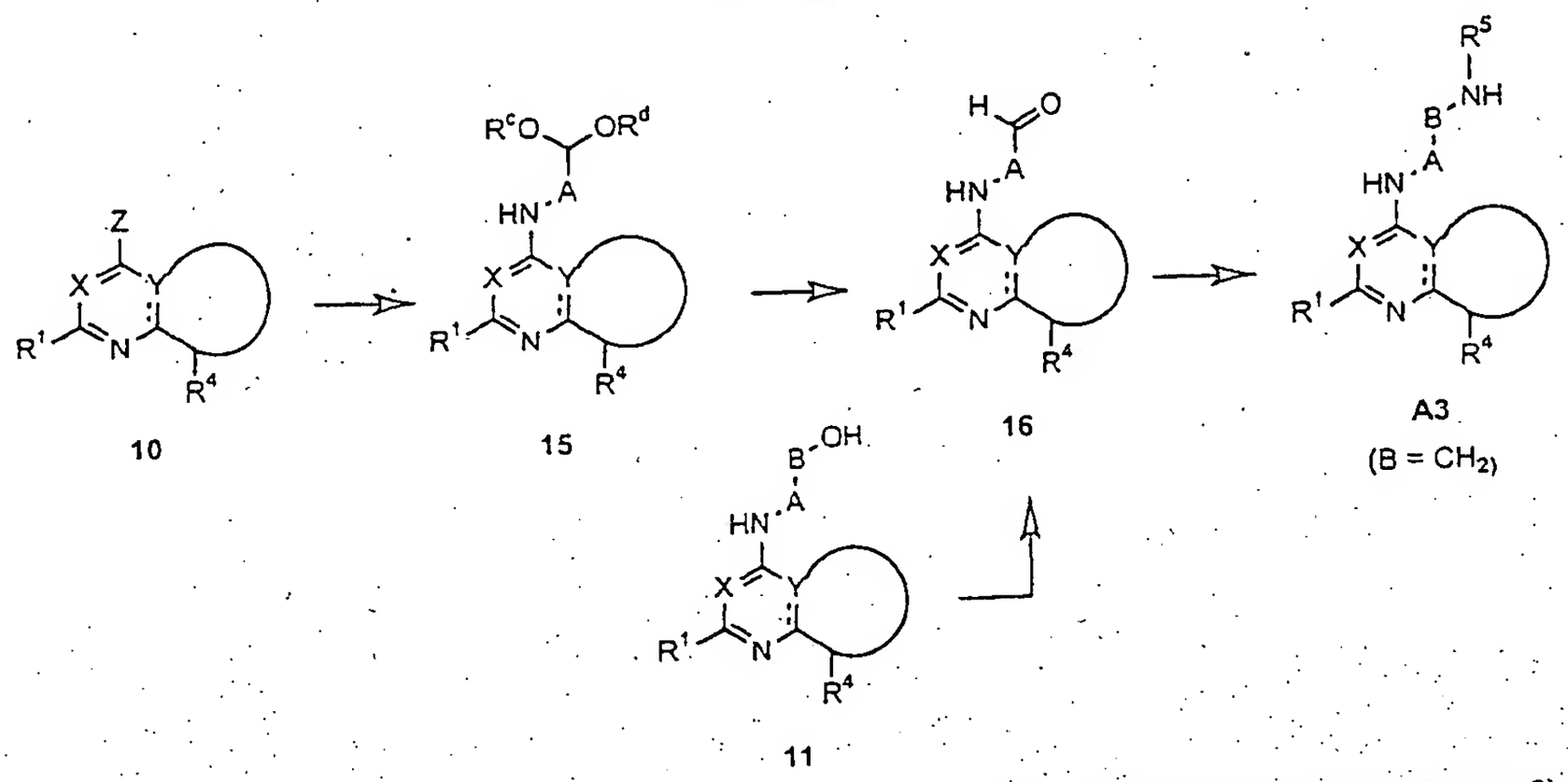
alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -78°C to 100°C.

SCHEME 5



Alternatively, a subset of compounds of formula A, described under formula A3 (scheme 5), can be obtained by first reacting a compound of formula **10** with an amine of formula H_2N-A-$CH(OR^c)(OR^d)$, where A is defined above, and R^c and R^d are C_1-C_6 lower alkyls or, taken together, complete a ketal group, such as, for example a dioxane or dioxolane group, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C to generate compounds of formula 15. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may

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include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably CH_2Cl_2). Compounds of formula 15 react with a protic acid in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C, followed by aqueous work-up to generate compounds of formula 16. Inert solvents may include, but are not limited to dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably CH_2Cl_2). Protic acids include, but are not limited to, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, methane sulfonic acid. Alternatively, compounds of formula 16 can be obtained by oxidation of compounds of formula 11 where B= CH_2. Oxidizing agents include, but are not limited to, transition metal oxides, such as CrO_3 or MnO_2, pyridine-chromium complexes, such as $CrO_3.C_5H_5N$, pyridinium dichromate or pyridinium chlorochromate, or an oxalyl chloride-DMSO-triethylamine reagent (Swern oxidation). Compounds of formula 16 react with amines of formula H_2N-R^5, where R^5 is defined above, in the presence of a reducing agent in the presence or absence of an inert solvent in the presence or absence of a protic acid at temperatures ranging from –78°C to 100°C, to give compounds of formula A3. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or

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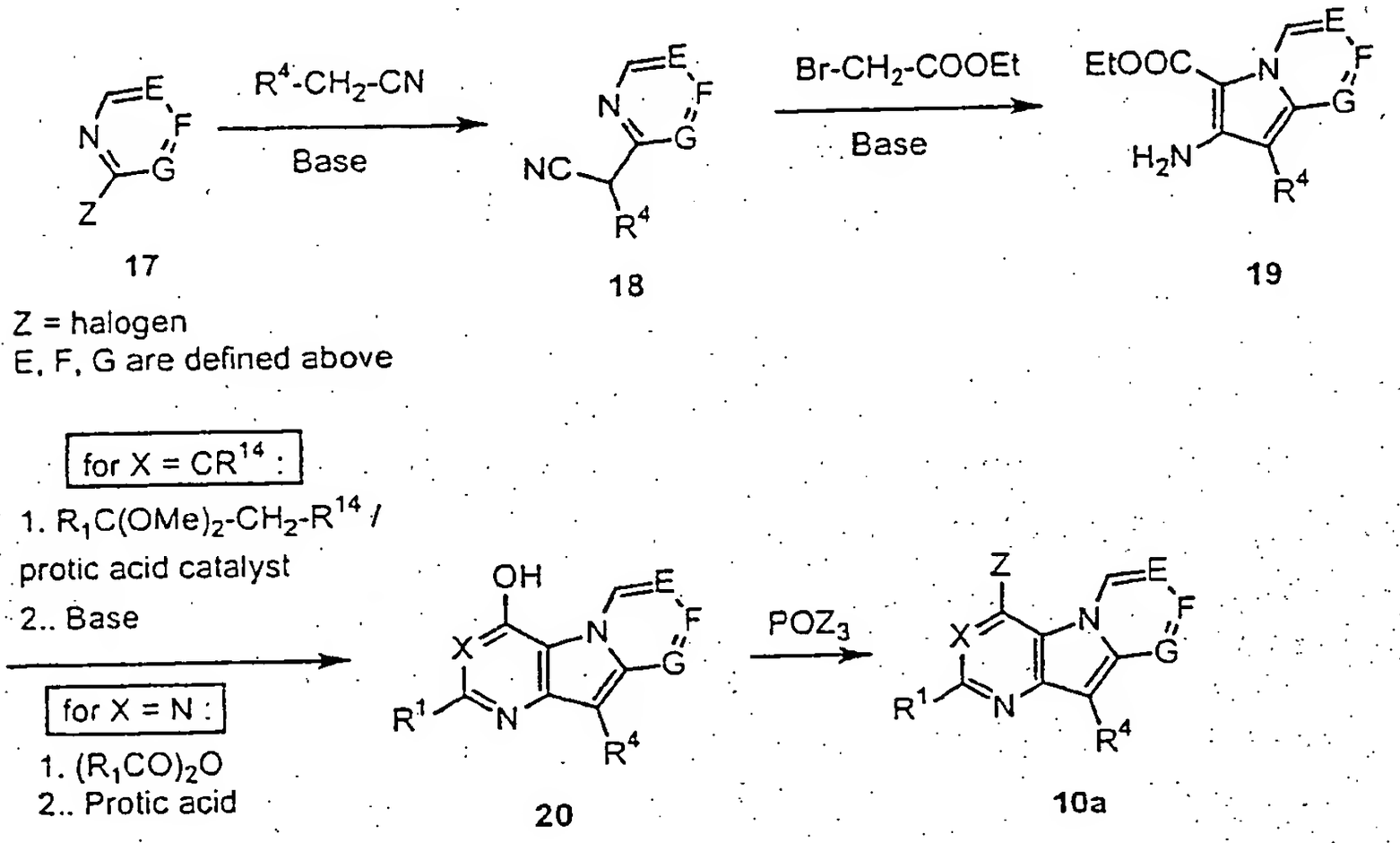
tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene).

Compounds of formula **10**, encompassing the heterocyclic cores of formula I-XV, are prepared according to procedures described in the references listed below.

Compounds of formula **10a**, used as starting material for the preparation of compounds of formula I, can be obtained according to scheme 6.

SCHEME 6



Compounds of formula 17, where E, F, and G are defined above and Z is a halogen, react with a compound of formula R^4-CH_2-CN, where R^4 is defined above, in the presence of base, in the presence or absence of an inert solvent, at reaction temperatures ranging from –78°C to 100°C, to generate compounds of formula 18. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-

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ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or dialkylsulfoxides (preferably dimethylsulfoxide). Preferred reaction temperatures range from 0°C to 100°C. Compounds of formula 18 then react with a compound of formula Z-CH_2-$COOR^c$, where Z is halogen (preferably chloro or bromo), alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and R^c is C_1-C_6 alkyl. in the presence of base, in the presence or absence of an inert solvent, at reaction temperatures ranging from –78 °C to 100°C, to generate compounds of formula 19. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or dialkylsulfoxides (preferably dimethylsulfoxide). Preferred reaction temperatures range from 0°C to 100°C. Compounds of formula 20, where X is CR^{14} and R^1 is defined above, can be obtained in two consecutive steps from compounds of formula 19 can be first reacted with a compound of formula $R^1C(OR^c)$-CH_2-R^{14}, where R^c is methyl or ethyl, in the presence of base, in the presence or absence of an inert solvent, at reaction temperatures ranging from –78°C to 100°C, to generate an non-isolated imine intermediate. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl

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alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or dialkylsulfoxides (preferably dimethylsulfoxide). Preferred reaction temperatures range from 0°C to 100°C. In a second step, the imine intermediates are cyclized to a compound of formula 20 ($X = CR^{14}$) in the presence of base, in the presence or absence of an inert solvent, at reaction temperatures ranging from –78°C to 100°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or dialkylsulfoxides (preferably dimethylsulfoxide). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of formula 20, where X is N and R^1 is defined above, can be obtained by reacting compounds of formula 19 with a compound of formula R^1-C=O-R^c, and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from –78°C to 200°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably

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dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Compounds of formula **10a**, where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is N, can be prepared by reacting a compound of formula 20 with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from –78°C to 250°C. Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably CH_2Cl_2). Preferred reaction temperatures range from -20°C to 100°C.

Alternatively, some of the compounds of formula A can be obtained from compounds of formula **21**, as illustrated in scheme 7.

SCHEME 7

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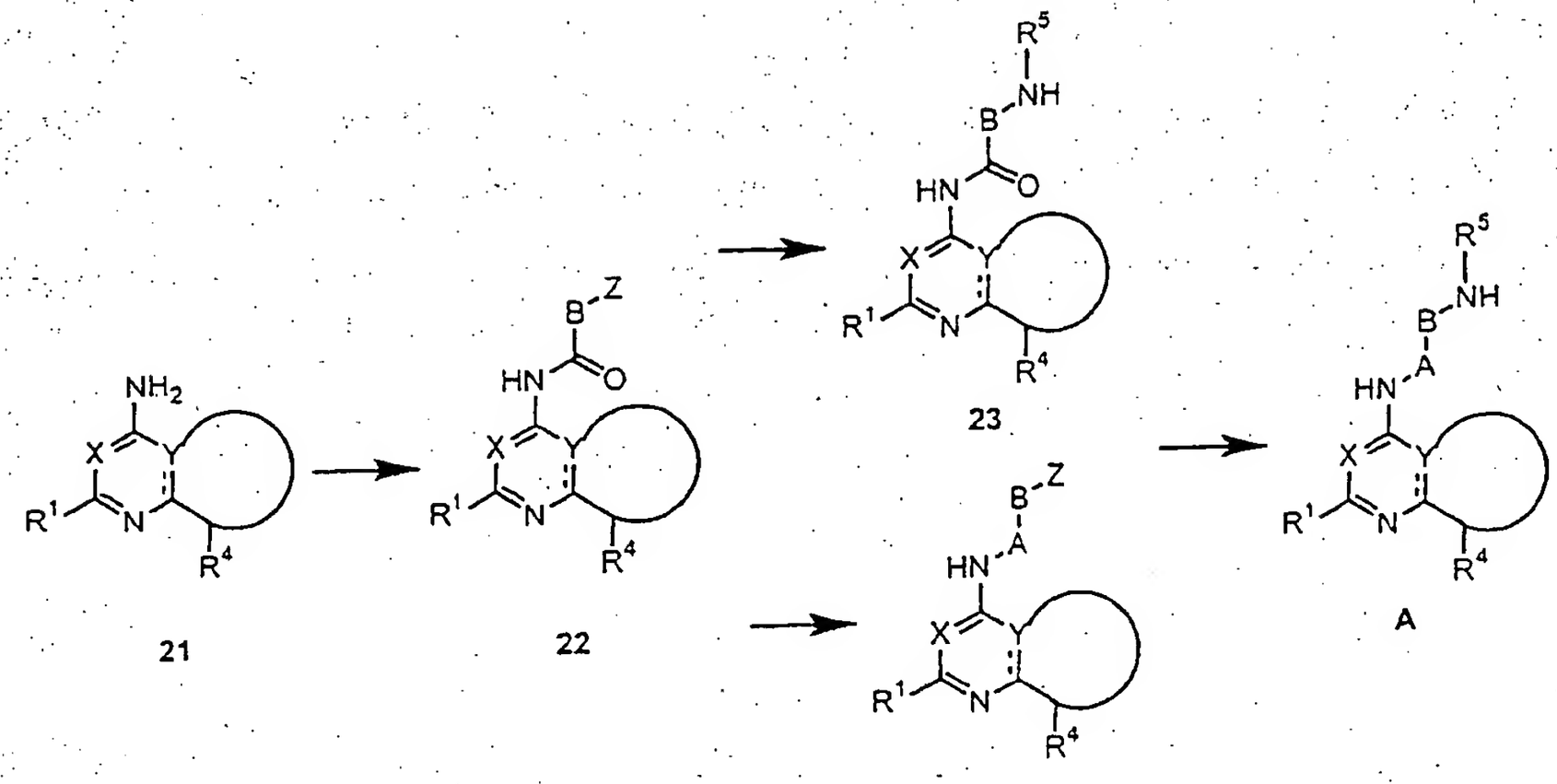

Compounds of formula 21 , where X, R^1 and R^4 are defined above, react with a compound of formula Z-B-(C=O)-R^c, where B is defined above, Z is halogen (preferably chloro or bromo), alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy, and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base, in the presence or absence of an inert solvent at reaction temperatures ranging from –78°C to 200°C, to produce compounds of formula 22. Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably CH_2Cl_2). Preferred reaction temperatures range from -20°C to 100°C.

Amides of formula 22 can be reacted with an amine of formula $NH[R^6]R^5$, where R^6 and R^5 are defined above, in the presence or absence of a base, in the presence or absence of an inert solvent at reaction temperatures ranging from –78°C to 200°C, to produce compounds of formula 23. Bases may include, but are not limited to, alkali metal hydrides

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(preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably CH_2Cl_2). Preferred reaction temperatures range from 0°C to 140°C.

Compounds of formula 23 can be reacted with a reducing agent in the presence or absence of an inert solvent to provide compounds of formula A, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -78°C to 100°C.

Alternatively, compounds of formula 22 can be reduced first, under experimental conditions similar to those used for the conversion of compounds of formula 23 to compounds of formula A, to generate compounds of formula 24. Compounds of formula 24 can then be reacted with compounds of formula $NH[R^6]R^5$, as defined above, under experimental conditions similar to those used for the conversion of compounds of formula 22 to compounds of formula 23, to generate compounds of formula A.

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Other compounds of formula 10 and of formula 21, used as starting material for the preparation of compounds of formula II-XV, can be obtained according to procedures described in the following references:

Formula II : WO 9413676, WO 9534563, WO 9845295, EP 729758, *J. Med. Chem.*, 40(11), 1749-1754 (1997), *Bioorg. Med. Chem. Lett.*, 9(7), 967-972 (1999), *J. Med. Chem.*, 42(5), 819-832 (1999) ; *J. Med. Chem.* 42(5), 833-848 (1999);

Formula III: WO 9635689, WO 9729110, WO 9808847, WO 9847903, WO 9940091, US 5664057;

Formula IV : WO 9413677, WO 9534563, EP 0729758;

Formula V: WO 9533750, *J. Med. Chem.* 42(5), 833-848 (1999); *Bioorg. Med. Chem. Lett.*, 9(7), 967-972 (1999);

Formula VI : WO 9808847, WO 9829397;

Formula VII: EP 239191, US 5273608;

Formula VIII: US 5273608;

Formula IX: WO 9510506, WO 9735539, WO 9808847, WO 9842706, *J. Med. Chem.* 42(5), 833-848 (1999);

Formula X : WO 9808847, WO 9835967;

Formula XI : WO 9533750, *Bioorg. Med. Chem. Lett.*, 9(7), 967-972 (1999);

Formula XII : WO 9808847, WO 9835967;

Formula XIII : WO 9744038;

Formula XIV : WO 9808846; WO 9829397, WO 9835967, WO 9847874, WO 9912908;

Formula XV : WO 9510506, WO 9533750, WO 9714684, WO 9735580, WO 9842699, EP 778277, *J. Med. Chem.* 39(22), 4358-4360 (1996), *J. Med. Chem.* 42(5), 805-818 (1999), *J. Med. Chem.* 42(5), 833-848 (1999).

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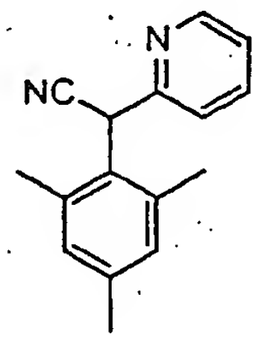
EXAMPLES

The following examples are which a provided to further illustrate the reaction schemes are not to be construed as limiting the invention.

The preparation of the compounds of the present invention by the above-mentioned methods is illustrated further by the following examples and those delineated in the Tables which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. Commercial reagents were used without further purification. THF refers to tetrahydrofuran. LDA refers to lithium diisopropylamide and DBU refers to 1,8-diazabicyclo[5.4.0]undec-7-ene. Room or ambient temperature refers to 20°C to 25°C. Concentration implies the use of a rotary evaporator. TLC refers to thin layer chromatography. Mass spectral data were obtained either by CI or APCI methods. Commonly used abbreviations arc: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, Bu is butyl, iBu is isobutyl (CH_2-$CHMe_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, MeOH means methanol, EtOH means ethanol, EtOAc means ethyl acetate, Et_2O means diethyl ether, CH_2Cl_2 means methylene chloride, DMSO means dimethyl sulfoxide, NMP means N-methyl pyrrolidone, THF means tetrahydrofuran, DMF means dimethyl formamide, EX means example. The specific heterocyclic cores, generically described under formula A, are indicated in the table under **Formula**, which refers to the heterocyclic core defined in formula I-XV.

EXAMPLE 1

A. 2-(2-Pyridinyl)-2-(2,4,6-trimethylphenyl)ethanenitrile



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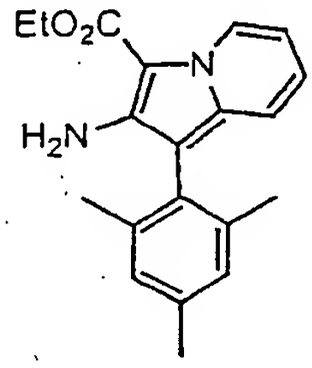
Add dropwise over a 1-hour period a mixed solution of 2-(2,4,6-trimethylphenyl)ethanenitrile (20 g; 0.126 mol) and 2-bromopyridine (35 g; 0.22 mol) in DMSO (25 mL) to a solution of potassium t-butoxide (35 g; 0.31 mol) dissolved in DMSO (125 mL). After the addition, stir the mixture for 4 h at ambient temperature and slowly pour into a stirred, ice-cold solution of NH_4Cl with vigorous stirring. Filter the resulting tan precipitate, wash with MeOH, and air-dry to obtain the title compound as a pale yellow solid : ^1H NMR (400MHz, $CDCl_3$) δ 2.30 (s, 6 H), 2.32 (s, 3 H), 5.76 (s, 1 H), 6.93 (s, 2 H), 7.12 (d, 1 H), 7.21 (dd, 1 H), 7.63 (t, 1 H), 8.63 (d, 1 H).

B. Ethyl 2-amino-1-(2,4,6-trimethylphenyl)indolizine-3-carboxylate



Slowly add dropwise ethyl bromoacetate (23mL; 0.21 mol) over a 3-hour period to a mixture of 2-(2-pyridinyl)-2-(2,4,6-trimethylphenyl)-ethanenitrile (22.3 g; 0.094 mol) and potassium carbonate (78 g; 0.57 mol) suspended in DMSO (100 mL). Stir the mixture for 1 day, pour into an aqueous NH_4Cl solution (ca. 1 L), and extract with 3 X 200 mL of Et_2O. Wash the combined extracts with saturated brine, dry over Na_2SO_4, filter, and concentrate *in vacuo*. Dissolve the residue in THF (200mL), cool to 0°C, and add slowly in portions potassium t-butoxide (12 g; 0.11 mol) over a 10-minute period. After 30 minutes at 0°C, dilute the mixture with aqueous NH_4Cl and extract with 2 X 150 mL of 50% Et_2O in hexane. Wash the combined extracts with saturated brine, dry over Na_2SO_4, filter, concentrate *in vacuo*, and purify by column chromatography on silica gel (eluent: 5 to 10% EtOAc in hexane) to obtain the title compound as an oil: ^1H NMR (400MHz, $CDCl_3$) δ 1.47 (t, 3 H), 2.06 (s, 6 H), 2.35 (s, 3 H), 4.46 (br q, 2 H), 6.6 (br t, 1 H), 6.75 (d, 1 H), 6.9 (br t, 1 H), 7.00 (s, 2 H), 9.4 (1 H).

C. 2-Methyl-9-(2,4,6-trimethylphenyl)pyrido[2,3-b]-indolizin-4-ol

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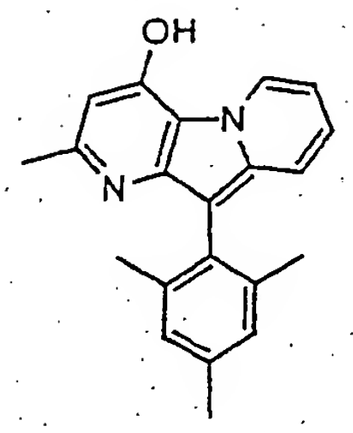
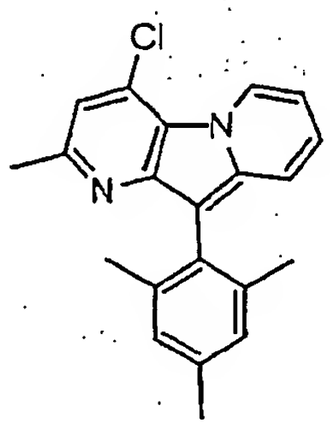


To a solution of 2-ethyl 2-amino-1-(2,4,6-trimethylphenyl)indolizine-3-carboxylate (19.2 g; 59.6 mmol) in 2,2-dimethoxypropane (100mL), add *dl*-camphorsulfonic acid (0.2g). Stir the mixture at reflux for 30 min and then distill slowly to remove *ca.* 60 mL of volatiles over a 30-minute period. Cool the solution to ambient temperature under inert atmosphere, dilute with anhydrous toluene (50mL), and concentrate *in vacuo*. Dissolve the residue in toluene (50mL) and add dropwise over a 1-hour period a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (250 mL; 125 mmol) to the stirred solution. After the addition, stir the mixture for 2 h at ambient temperature, concentrate *in vacuo* to a small volume and dilute with aqueous NH_4Cl. Filter the resulting biphasic mixture and wash successively with water, MeOH, and Et_2O. Dry under vacuum to obtain the title compound as a pale yellow solid.

D. 4-Chloro-2-methyl-9-(2,4,6-trimethylphenyl)pyridino[2,3-b]-indolizine



Heat at 100°C for 1 h a solution of 4-hydroxy-2-methyl-10-(2,4,6-trimethylphenyl)pyridino-[2,3-b]indolizine 2-methyl-9-(2,4,6-trimethylphenyl)pyrido[2,3-b]-indolizin-4-ol (10.1 g; 32 mmol) in phosphorus oxychloride (60 mL), cool to ambient temperature, and concentrate *in vacuo*. Partition the residue into ice water and CH_2Cl_2. Separate the aqueous phase, extract

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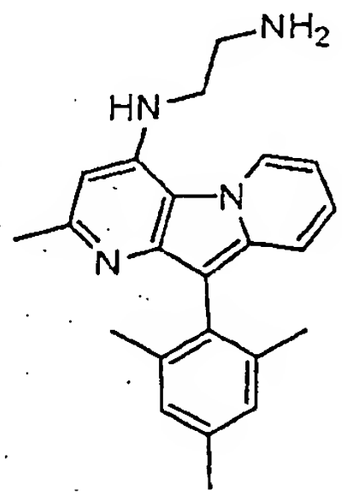
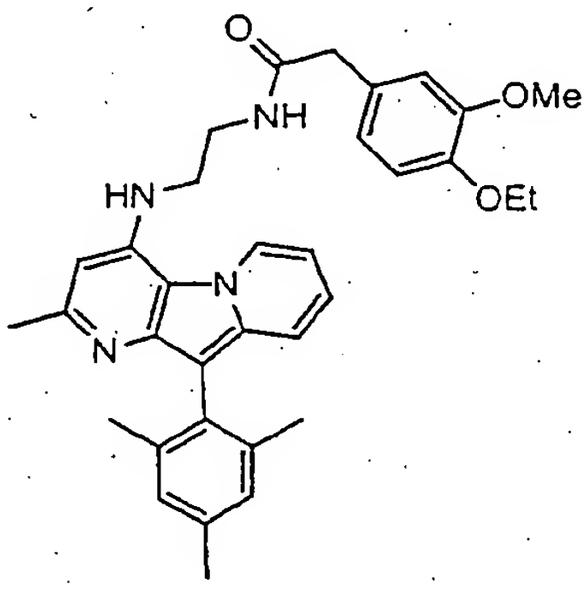
twice with CH_2Cl_2, and wash the combined organic extracts with a 1 N aqueous sodium hydroxide solution and then with water. Dry the solution over Na_2SO_4, filter, and concentrate *in vacuo*. Filter the dark residue through a short pad of silica gel and wash with 25% EtOAc in hexane. Concentrate the filtrate *in vacuo* to obtain the title compound as a yellow solid : ^1H NMR (400MHz, $CDCl_3$) δ 2.00 (s, 6 H), 2.37 (s, 3 H), 2.64 (s, 3 H), 6.58 (t, 1 H), 6.95 (dd, 1 H), 7.00 (s, 2 H), 7.07 (s, 1 H), 7.08 (d, 1 H), 9.26 (d, 1 H).

E. (2-Aminoethyl)[2-methyl-9-(2,4,6-trimethylphenyl)-pyridino[2,3-b]indolizin-4-yl]amine



Heat a solution of 4-chloro-2-methyl-9-(2,4,6-trimethylphenyl)pyridino[2,3-b]-indolizine (0.35g, 1.04 mmol), and ethylene diamine (0.32 g, 1.04 mmol) in dry NMP (3mL) at 100 °C for 5 h. Pour the cooled mixture onto water (30 mL) and extract twice with EtOAc (30 mL). Wash the combined extract with brine (30 mL), dry, and evaporate *in vacuo*. Purify by preparative TLC (20 % MeOH in CH_2Cl_2 with 1% ammonium hydroxide) to obtain the title compound as a colorless oil.

F. 2-(4-Ethoxy-3-methoxy-phenyl)-N-{2-[2-methyl-9-(2,4,6-trimethyl-phenyl)-pyridino[2,3-b]indolizin-4-ylamino]-ethyl}-acetamide



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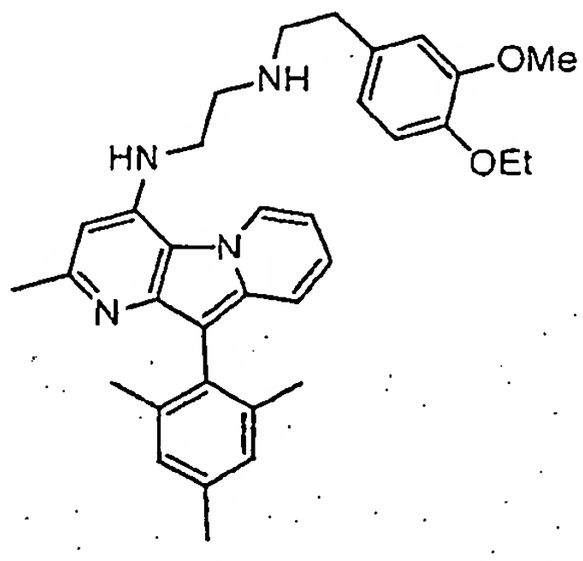
Treat a solution of (2-aminoethyl)[2-methyl-9-(2,4,6-trimethylphenyl)-pyridino[2,3-b]indolizin-4-yl]amine (0.08g, 0.22mmol), 4-ethoxy, 3 methoxy phenylacetic acid (0.05 g, 0.22 mmol) and N,N diisopropylethyl amine (0.04 mL, 0.24mmol) in CH_2Cl_2 (10 mL) with benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (0.1 g, 0.24 mmol) and stir at ambient temperature for 14 h. Dilute the resulting mixture with CH_2Cl_2 (20 mL), water (20 mL), and saturated aq NaCl (20 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by preparative TLC (10% MeOH in CH_2Cl_2) to obtain the title compound as a solid.

G. (2-{[2-(4-Ethoxy-3-methoxyphenyl)ethyl]amino}ethyl)[2-methyl-9-(2,4,6-trimethylphenyl)pyridino[2,3-b]indolizin-4-yl]amine



Treat a solution of 2-(4-ethoxy-3-methoxy-phenyl)-N-{2-[2-methyl-9-(2,4,6-trimethyl-phenyl)-pyridino[2,3-b]indolizin-4-ylamino]-ethyl}-acetamide (0.08 g, 0.145 mmol) in THF (5 mL) with $AlH_3.NMe_2Et$ (3 mL, 1.45 mmol) and heat to reflux for 14 h. Cool the resulting mixture to ambient temperature, quench with $Na_2CO_3.10H_20$ (0.3 g) and stir at ambient temperature for 15 min. Filter the solution through Celite and wash with several portions of CH_2Cl_2. Concentrate the filtrate *in vacuo* to dryness and purify by preparative TLC (10 % MeOH in CH_2Cl_2 with 0.5 % ammonium hydroxide) to the title compound as a solid.

EXAMPLE 2

A. 2-Methyl-9-(2,4,6-trimethylphenyl)pyrimidino[4,5-b]indolizin-4-ol

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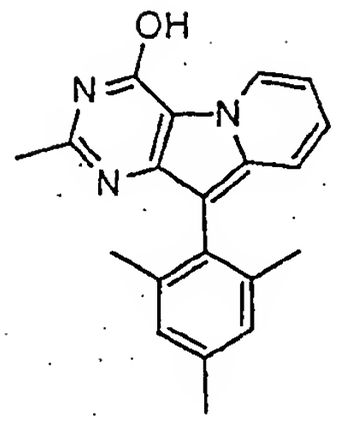
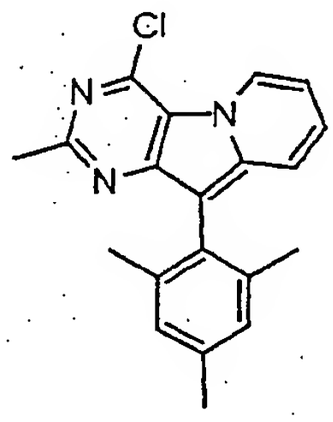


Heat to 100°C for 1 h a solution of 2-amino-3-cyano-1-(2,4,6-trimethylphenyl)indolizine (220 mg) in an acetic anhydride (0.5 mL) - acetic acid (2 mL) mixture. Cool the mixture to ambient temperature before concentrating in vacuo. Heat the residue in 85% phosphoric acid (5mL) at 100°C for 1.5 h, allow to cool to ambient temperature, dilute with water, and neutralize to pH 7 by adding aqueous NaOH. Extract the resulting yellow suspension twice with CH_2Cl_2 and dry the combined extracts on Na_2SO_4, filter, concentrate, and purify by column chromatography on silica gel (eluent: 50% EtOAc in hexane to 10% MeOH in EtOAc) to obtain the title compound as a yellow solid.

B. 4-Chloro-2-methyl-9-(2,4,6-trimethylphenyl)pyrimidino[4,5-b]indolizine



Heat at 100°C for 2 h a solution of 2-methyl-9-(2,4,6-trimethylphenyl)pyrimidino[4,5-b]indolizin-4-ol (120 mg) in phosphorus oxychloride (2 mL), cool to ambient temperature, and concentrate *in vacuo*. Partition the residue into ice water and CH_2Cl_2. Extract the aqueous phase twice with CH_2Cl_2 and wash the combined organic extracts with a saturated $NaHCO_3$ solution. Dry the solution over Na_2SO_4, filter, and concentrate *in vacuo*. Purify the dark residue by column chromatography on silica gel (eluent: 10% to 20% EtOAc in hexane)

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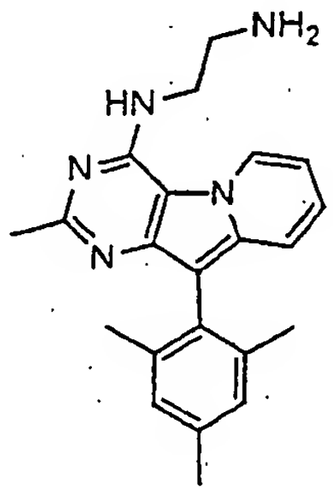
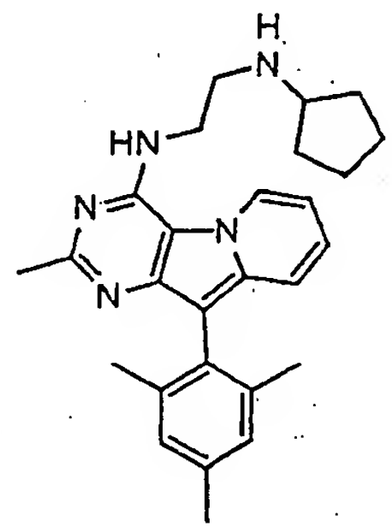
to obtain the title compound as a greenish yellow foam : ^{1}H NMR (400MHz, $CDCl_3$) δ 1.99 (s, 6 H), 2.38 (s, 3 H), 2.79 (s, 3 H), 6.80 (m, 1 H), 7.00 (s, 2 H), 7.19 (m, 2 H), 9.27 (d, 1 H).

C. (2-Aminoethyl)[2-methyl-9-(2,4,6-trimethylphenyl)pyrimidino[4,5-b]indolizin-4-yl]amine



Heat a solution of 4-chloro-2-methyl-9-(2,4,6-trimethylphenyl)pyrimidino[4,5-b]indolizine (0.3 g, 0.89 mmol), and ethylene diamine (0.6 mL, 8.93 mmol) in dry NMP (3mL) at 100 ^{0}C for 14 h. Pour the cooled mixture onto water (30 mL) and extracte twice with EtOAc (30 mL). Wash the combined extracts with brine (30 mL), dry, and evaporate *in vacuo*. Purify by preparative TLC (20 % MeOH in CH_2Cl_2 with 0.5% ammonium hydroxide) to obtain the title compound as a yellow oil.

D. [2-(Cyclopentylamino)ethyl][2-methyl-9-(2,4,6-trimethylphenyl)pyrimidino[4,5-b]indolizin-4-yl]amine



Treat a solution of (2-aminoethyl)[2-methyl-9-(2,4,6-trimethylphenyl)pyrimidino[4,5-b]indolizin-4-yl]amine (0.07 g, 0.19 mmol), cyclopentanone (0.02 mL, 0.19 mmol) and acetic acid (0.01 mL, 0.19 mmol) in dry dichloroethane (3 mL) with sodium triacetoxyborohydride (0.06g, 0.27 mmol) and stir at ambient temperature for 14 h. Dilute the resulting mixture

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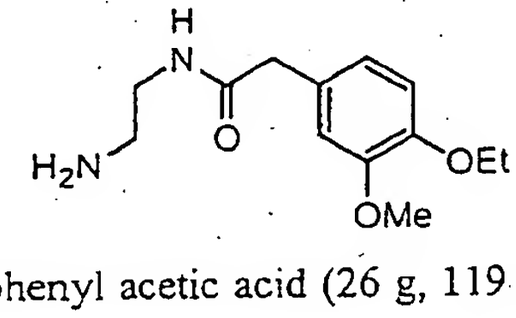
with CH_2Cl_2 (20 mL) and wash with saturated aq NaCl (50 mL). Dry the organic portion over Na_2SO_4, filter, and concentrate under reduced pressure. Purify by preparative TLC (10 % MeOH in CH_2Cl_2 with 0.5 % ammonium hydroxide) to obtain the title compound as a yellow solid.

EXAMPLE 3

A. N-(2-Amino-ethyl)-2-(4-ethoxy-3-methoxy-phenyl)-acetamide.



Dissolve 4-ethoxy-3-methoxy-phenyl acetic acid (26 g, 119 mol) in dichloroethane (300 mL, anhydrous) and cool to 0°C. Dropwise add oxalyl chloride (130 mL, 2.0 M in CH_2Cl_2) and DMF (2 mL), then allow to warm to ambient temperature for 14 h. Concentrate under reduced pressure to a tan oil. Dissolve in dichloroethane (200 mL) and cool to 0°C while stirring under N_2. Dropwise, over 45 minutes, add a second solution of N-tBOC-ethylenediamine (20 g) and triethylamine (20 mL) in dichloroethane (100 mL). Partition between CH_2Cl_2 (500 mL) and 1.0 N HCl (200 mL), separate the layers, and wash the organic phase with 1.0 N HCl (200 mL). Wash the organic layer with saturated K_2CO_3 (2 X 200 mL), then dry the CH_2Cl_2 layer over Na_2SO_4, filter, and evaporate to tan solid. Triturate with Et_2O (200 mL) and stir vigorously to fragment solid, then filter and wash copiously with Et_2O to obtain a white solid. Dissolve the white solid (3.0 g, 8.52 mmol) in a 1:1 mixture of trifluoracetic acid and CH_2Cl_2 (10 mL) and stir at ambient temperature 1 h. Concentrate under reduced pressure and partition between CH_2Cl_2 (25 mL) and 1.0 N NaOH (25 mL), then separate the layers, and extract the aqueous layer with CH_2Cl_2 (25 mL). Pool the organic layers, dry over Na_2SO_4, filter and concentrate *in vacuo* to a white solid.

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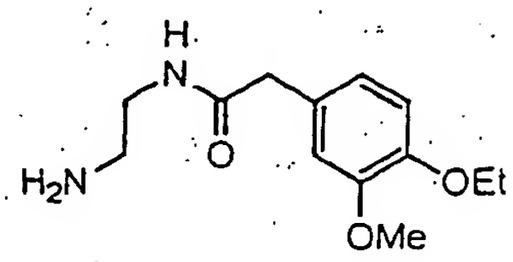
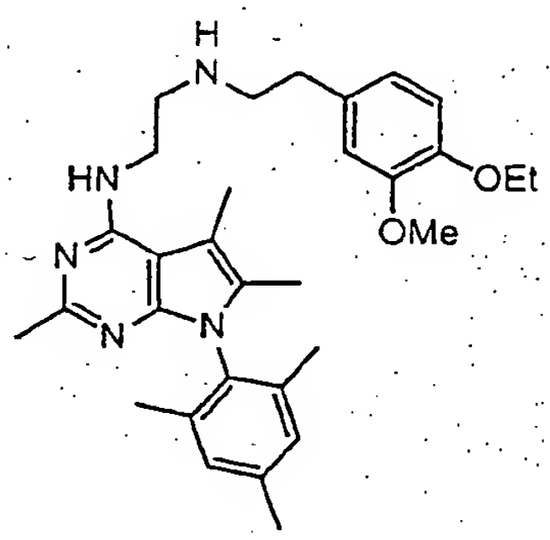
B. N-(4-Ethoxy-3-methoxy-phenethyl)-ethylenediamine



Treat a solution of N-(2-amino-ethyl)-2-(4-ethoxy-3-methoxy-phenyl)acetamide (0.7 g, 2.77 mmol) in THF (10 mL) with $AlH_3.NMe_2Et$ (55 mL, 27.74 mmol) and heat to reflux for 14 h. Cool the resulting mixture to ambient temperature, quench with $Na_2CO_3.10H_20$ (0.5 g) and stir at ambient temperature for 15 min. Filter the solution through Celite and wash with several portions of CH_2Cl_2. Concentrate the filtrate in vacuoo and purify by preparative TLC (10 % MeOH in CH_2Cl_2) to obtain the title compound as a white oil.

C. (2-{[2-(4-Ethoxy-3-methoxyphenyl)ethyl]amino}ethyl)[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-yl]amine



Heat a solution of 4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine (340 mg, 1.1 mmol) and N-(4-ethoxy-3-methoxy-phenethyl)-ethylenediamine in NMP (2 mL) for 14 h at 130°C. Pour into water (5 mL) and extract with EtOAc (2 X 10 mL). Dry the combined organic extracts over Na_2SO_4 , filter, and concentrate under reduced pressure. Purify by preparative TLC, eluting with 10% MeOH in CH_2Cl_2. Dissolve the residue in a minimum amount of MeOH then add HCl in EtOAc (2 mL) and triturate with Et_2O to obtain the title compound as a solid (HCl salt).

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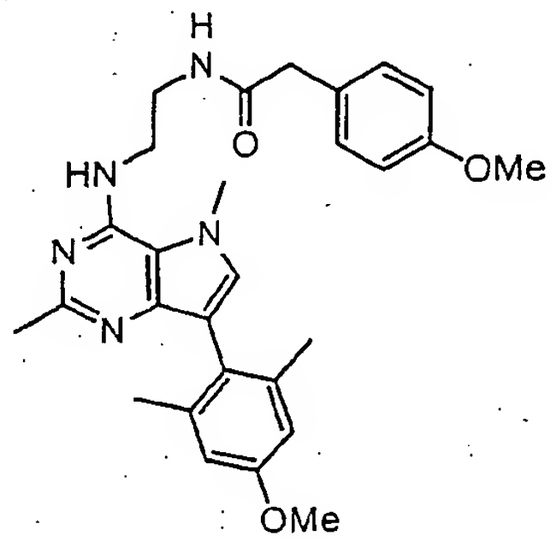
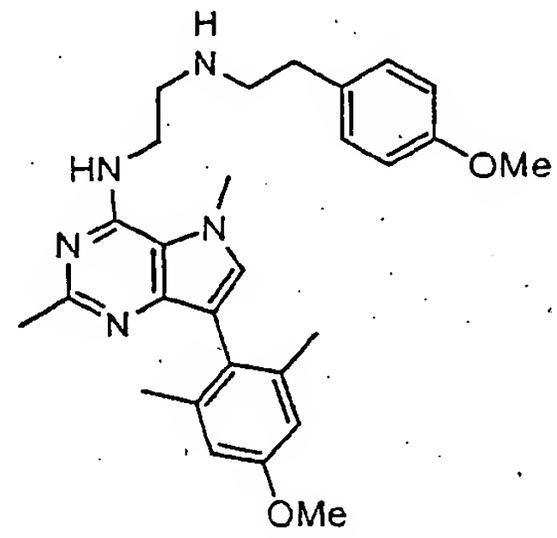
EXAMPLE 4

A. 2-(4-Methoxyphenyl)-N-(2-{[7-(4-methoxy-2,6-dimethylphenyl)-2,5-dimethylpyrrolo[2,3-e]pyrimidin-4-yl]amino}ethyl)acetamide



Heat a solution of 4-chloro-7-(4-methoxy-2,6-dimethyl-phenyl)-2,5-dimethyl-5H-pyrrolo[3,2-d]pyrimidine (120 mg, 0.38 mmol) and N-(2-amino-ethyl)-2-(4-methoxy-phenyl)-acetamide (125 mg) in NMP (2 mL) for 14 h at 130°C. Pour into water (5 mL) and extract with EtOAc (2 X 10 mL). Dry the combined organic extracts over Na_2SO_4 , filter, and concentrate under reduced pressure to obtain the title compound which is used without further purification.

B. (2-{[2-(4-Methoxyphenyl)ethyl]amino}ethyl)[7-(4-methoxy-2,6-dimethylphenyl)-2,5-dimethylpyrrolo[2,3-e]pyrimidin-4-yl]amine



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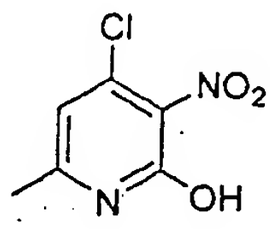
Dissolve 2-(4-methoxyphenyl)-N-(2-{[7-(4-methoxy-2,6-dimethylphenyl)-2,5-dimethylpyrrolo[2,3-e] pyrimidin-4-yl]aminoethyl)acetamide in anhydrous THF (5 mL) and stir under N_2. Add borane-dimethylsulfide complex (0.2 mL, 10.0 M in THF) and heat to reflux for 14 h. Quench by addition of N,N'-dimethyl-1,2-ethylenediamine (0.21 mL) in MeOH (5 mL) and stir for 1 h at ambient temperature. Concentrate under reduced pressure and purify the residue by preparative TLC, eluting with 10% MeOH in CH_2Cl_2. Dissolve the residue in a minimum amount of MeOH then add HCl in EtOAc (2 mL) and triturate with Et_2O to obtain the title compound as a solid (HCl salt).

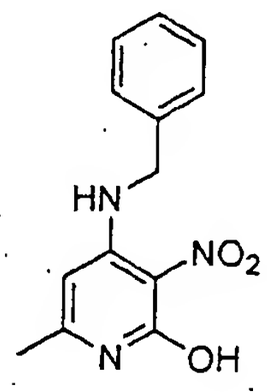
EXAMPLE 5

A. 4-Chloro-6-methyl-3-nitro-pyridin-2-ol



Add 1-ethylpropylamine (9.00 g, 76.4 mmol) to a solution of 4-hydroxy-6-methyl-3-nitropyridone (10.0 g, 58.8 mmol) in anhydrous MeOH (20 mL). Stir the mixture until clear, then concentrated *in vacuo*. Add the residue portionwise to phosphorus oxychloride (70 mL), Stir at ambient temperature for 10 h, and pour onto ice-water. After stirring for 20 min, filter the precipitate, and dry over Na_2SO_4 to obtain the title compound as a yellow solid.

B. 4-Benzylamino-6-methyl-3-nitro-pyridin-2-ol



Stir a solution of 4-chloro-6-methyl-3-nitro-pyridin-2-ol (10.0 g, 53.0 mmol) and benzyl amine (17.3 g, 159 mmol) in EtOH (30 mL) at ambient temperature for 12 h, then concentrate

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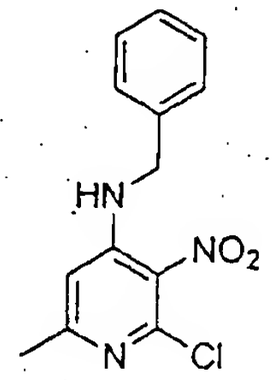
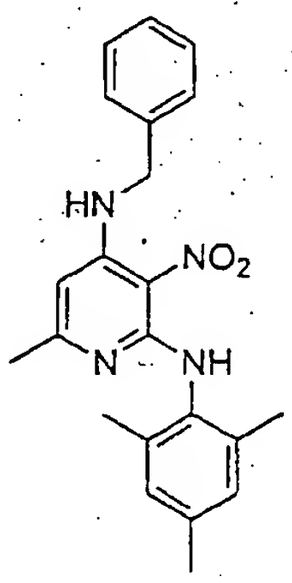
in vacuo. Pour the resulting residue into water, acidify to pH 3 with 1N HCl and filter. Wash the precipitate several times with water to obtain the title compound as a yellow solid.

C. 4-Benzylamino-6-methyl-3-nitro-2-chloro-pyridine



Heat a solution of 4-benzylamino-6- methyl-3-nitro-pyridin-2-ol (13.70 g, 52.8 mmol) and tetramethylammonium chloride (6.0 g, 52.8 mmol) to reflux in phosphorus oxychloride (15 mL) for 5 h. After cooling, remove the excess phosphorus oxychloride *in vacuo*. Triturate the residue in ice-water (400 mL) to obtain the title compound as a brown solid.

D. 6-Methyl-3-nitro-4-[benzylamino](2-pyridyl)}(2,4,6-trimethylphenyl)amine



Add *p*-toluene sulfonic acid (11.0 g, 56.3 mmol) to a solution of 4-benzylamino-6-methyl-3-nitro-2-chloro-pyridine (13.0 g, 46.8 mmol) and 2,4,6-trimethylaniline (6.58 g, 46.8 mmol) in 350 mL of toluene. Heat the resulting mixture for 14 h under reflux using a Dean-Stark trap. After cooling to ambient temperature, dilute the solution with EtOAc (200 mL) and wash successively with saturated aq $NaHCO_3$ and saturated aq NaCl . Separate the organic layer, dry over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by flash column

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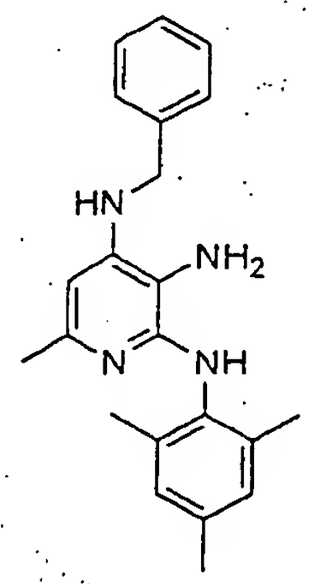
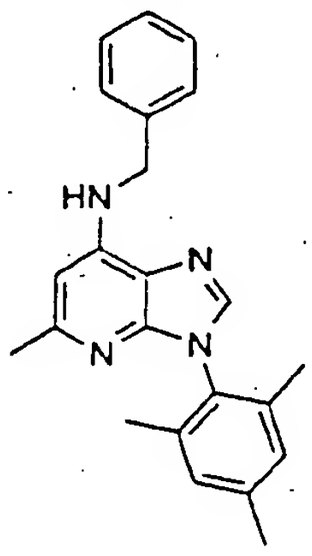
chromatography (2% methanol in CH_2Cl_2) to obtain obtain the title compound as a dark yellow solid.

E. 3-Amino-6-methyl-4-[benzylamino](2-pyridyl)(2,4,6-trimethylphenyl)amine



Add iron powder (7.0 g) to a solution of 6-methyl-3-nitro-4-[benzylamino](2-pyridyl)(2,4,6-trimethylphenyl)amine (8.75 g, 23.2 mmol) in acetic acid (14 mL) and MeOH (70 mL). Heat the resulting mixture at 70°C for 1 h, cool to ambient temperature, and filter through a pad of celite. Evaporate the filtrate to dryness under reduced pressure. Treat he residue with 1N aq NaOH and extract with EtOAc . Wash the EtOAc extract with water and saturated aq NaCl . Separate the organic layer, dry over Na_2SO_4, filter, and concentrate to obtain the title compound as a brown solid which is used without further purification.

F. [5-methyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]benzylamine



Treat a solution of 3-amino-6-methyl-4-[benzylamino](2-pyridyl)(2,4,6-trimethylphenyl)amine (0.80 g, 2.31 mmol) and triethyl orthoformate (8.0 mL, 48.5 mmol) in dimethylacetamide (9 mL) with 12 M HCl (0.4 mL). Stir the mixture at ambient

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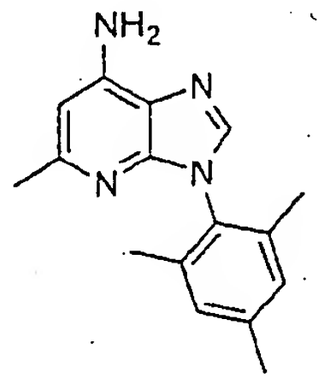
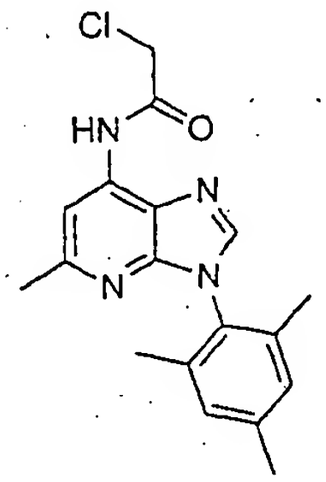
temperature for 14 h, dilute with EtOAc (50 mL), and wash with aq $NaHCO_3$ (50 mL) and saturated aq NaCl (50 mL). Dry the organic layer over Na_2SO_4, filter, and concentrate. Purify by preparative TLC (10 % methanol in CH_2Cl_2 with 0.1% ammonium hydroxide) to obtain the title compound as a solid.

G. 5-methyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-ylamine



Add palladium hydroxide (0.05 g) to a solution of [2,5-dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]benzylamine (0.15g , 0.42 mmol) in acetic acid (10 mL). Hydrogenate the mixture at a pressure of 50 psi for 20 hr. Filter the reaction mixture through celite, evaporate to dryness under reduced pressure, dilute with EtOAc and successively wash with aq $NaHCO_3$ and aq NaCl. Dry the organic layer over Na_2SO_4, filter, and concentrate. Purify by flash column chromatography (3% MeOH in CH_2Cl_2) to obtain the title compound as a brown solid.

H. N-[5-methyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]-2-chloroacetamide



Treat a solution of 5-methyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-ylamine (0.05 g, 1.9 mmol), and N,N-diisopropylethylamine, (0.04 mL, 0.21 mmol) in 1, 2-dichloroethane (5 mL) with chloroacetyl chloride (0.017 mL, 0.21mmol). Heat the solution to reflux for 3 h, cool to ambient temperature, and pour into an aqueous potassium carbonate

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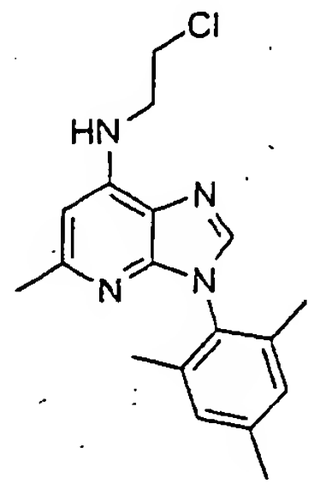
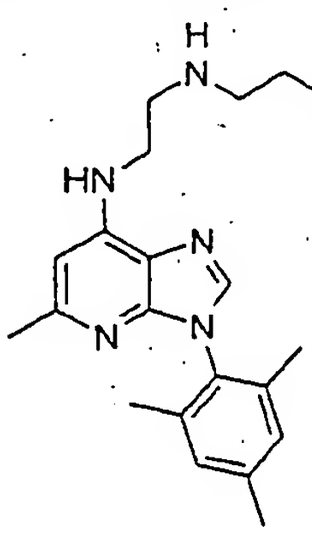
solution. Extract the resulting mixture with CH_2Cl_2 and wash with saturated aq NaCl. Separate the organic layer, dry over Na_2SO_4, filter, and concentrate. Purify by preparative TLC (5 % MeOH in CH_2Cl_2) to obtain the title compound as a yellow solid.

I. (2-Chloroethyl)[5-methyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]-amine



Treat a solution of N-[5-methyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]-2-chloroacetamide (0.04 g, 0.10 mmol) in THF (5mL) with borane-methyl sulfide complex (0.03 mL, 0.30 mmol). Heat the mixture to reflux for 8 h and quench at ambient temperature with a large excess of MeOH, followed by 6 N HCl (2 mL). Re-heat the mixture to reflux for 1 h, then concentrate under reduced pressure to obtain the title compound as a yellow solid.

J. (2-{[2-(4-Ethoxy-3-methoxyphenyl)ethyl]amino}ethyl)[5-methyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]amine



Heat a solution of (2-chloroethyl)[5-methyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]-amine (0.030 g, 0.09 mmol) and 4-ethoxy-3-methoxy phenethylamine (0.10 g, 0.55 mmol) in dry NMP (2 mL) at 110^{0}C for 16 h. Pour the cooled mixture onto water (20

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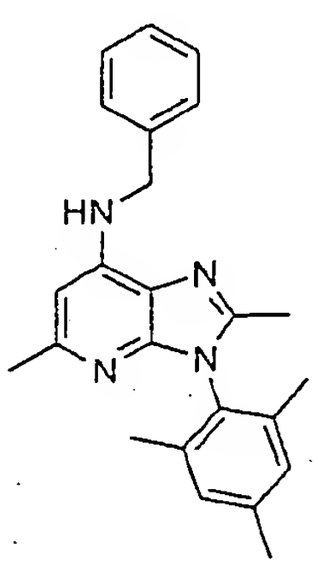
mL) and extract twice with EtOAc (20 mL). Wash the combined extracts with brine (30 mL), dry, and evaporate *in vacuo*. Purify by flash column chromatography (10% MeOH in CH_2Cl_2 with 0.1% ammonium hydroxide) to obtain the title compound as a solid.

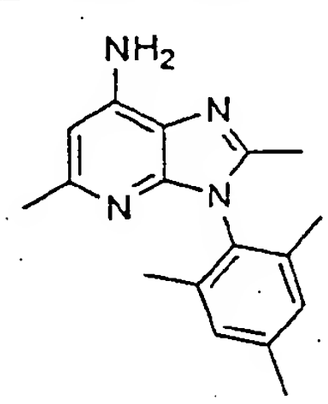
EXAMPLE 6

A. [2,5-dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]benzylamine



Heat a solution of 3-amino-6-methyl-4-[benzylamino](2-pyridyl)(2,4,6-trimethylphenyl)amine (2.50 g, 7.21 mmol), tricthyl orthoacetate (2.6 mL, 14.4 mmol) and camphorsulfonic acid (250 mg) in toluene (50 mL) to reflux for 14 h. After cooling to ambient temperature, concentrate the mixture *in vacuo*, dilute with water (100 mL), and extract with EtOAc. Wash the EtOAc extract successively with water and saturated aq NaCl, dry over Na_2SO_4, filter, and concentrate. Purify by flash column chromatography (5% methanol in CH_2Cl_2) to obtain the title compound as a white solid.

B. 2,5-Dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridine-7-ylamine



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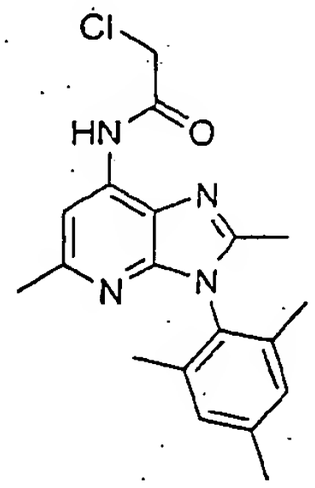
Add palladium hydroxide (2.0 g) to a solution of [2,5-dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]benzylamine (1.50 g , 4.05 mmol) in acetic acid (10 mL). Hydrogenate the mixture at a pressure of 40 psi for 20 hr. Filter the reaction mixture through celite, evaporate to dryness under reduced pressure, dilute with EtOAc and successively wash with aq. $NaHCO_3$ and aq NaCl. Dry the organic layer over Na_2SO_4, filter, and concentrate. Purify by flash column chromatography (3% MeoH in CH_2Cl_2) to obtain the title compound as a white solid.

C. N-[2,5-Dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]-2-chloroacetamide



Treat a solution of 2,5-dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridine-7-ylamine (0.8 g, 2.85 mmol), and N,N-diisopropylethylamine, (0.54 mL, 3.13 mmol) in 1, 2-dichloroethane (10 mL) with chloroacetyl chloride (0.25 mL, 3.13mmol). Heat the solution to reflux for 5 h, cool to ambient temperature, and pour into an aqueous potassium carbonate solution. Extract the resulting mixture with CH_2Cl_2 and wash with saturated aq NaCl. Separate the organic layer, dry over Na_2SO_4, filter and concentrate. Purify by preparative TLC (5 % MeOH in CH_2Cl_2) to obtain the title compound as a brown solid.

D. [2,5-Dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl](2-chloroethyl)amine

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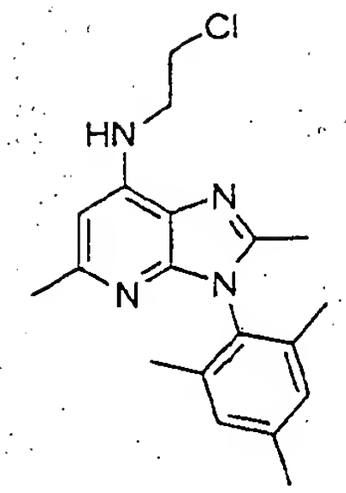
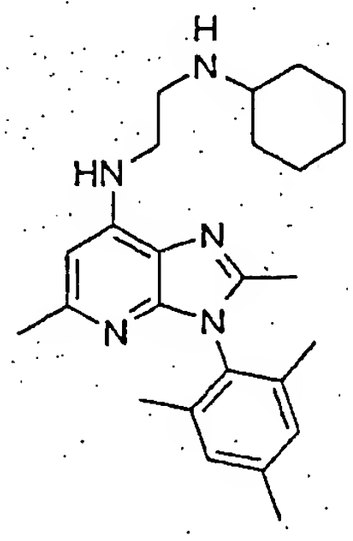


Treat a solution of N-[2,5-dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl]-2-chloroacetamide (0.91g, 2.55 mmol) in THF (5mL) with borane-methyl sulfide complex (0.8 mL, 7.65 mmol). Heat the mixture to reflux for 18 h and quench at ambient temperature with a large excess of MeOH, followed by 6N HCl (5 mL). Re-heat the mixture to reflux for 1 h, then concentrate under reduced pressure to obtain the title compound as a white crystalline solid.

E. [2,5-Dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl][2-(cyclohexylamino)ethyl]amine



Heat a solution of [2,5-dimethyl-3-(2,4,6-trimethylphenyl)imidazolo[5,4-b]pyridin-7-yl](2-chloroethyl)amine (0.04 g, 0.12 mmol), and cyclohexyl amine (0.13 mL g, 1.16 mmol) in dry NMP (2 mL) at 80 °C for 20 h. Pour the cooled mixture onto water (20 mL) and extract twice with ethyl acetate (20 mL). Wash the combined extracts with brine (20 mL), dry, and evaporate *in vacuo*. Purify by flash column chromatography (10% methanol in CH_2Cl_2 with 0.1% ammonium hydroxide) to obtain the title compound as a white solid.

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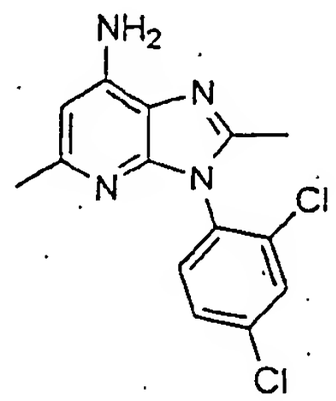
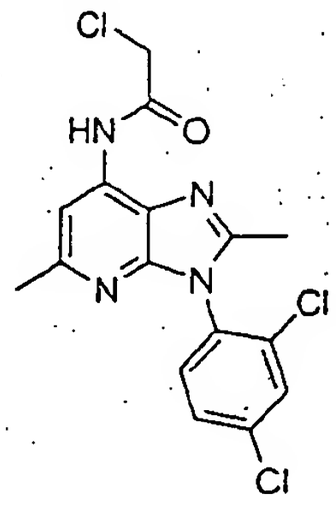
EXAMPLE 7

A. 3-(2,4-dichlorophenyl)-2,5-dimethylimidazolo[5,4-b]pyridin-7-ylamine



Stir a solution of [3-(2,4-dichlorophenyl)-2,5-dimethylimidazolo[5,4-b]pyridin-7-yl](4-methoxybenzyl)amine (4.23 g, 10 mmol), anisole (3.2 mL, 29.6 mmol), trifluoroacetic acid (80 mL), and concentrated sulfuric acid (2 mL) at ambient temperature for 14 h. Add the resulting mixture dropwise to ice-water and dilute with $NaHCO_3$. Filter the resulting precipitate and wash thoroughly with water to obtain the title compound as a brown solid.

B. N-[3-(2,4-dichlorophenyl)-2,5-dimethylimidazolo[5,4-b]pyridin-7-yl]-2-chloroacetamide



Treat a solution of 3-(2,4 -dichlorophenyl)-2,5-dimethylimidazolo[5,4-b]pyridin-7-ylamine (0.2 g, 0.65 mmol), and N,N-diisopropylethylamine, (0.12 mL, 0.72 mmol) in 1, 2-dichloroethane (10 mL) with chloroacetyl chloride (0.06 mL, 30.72 mmol). Heat the solution to reflux for 2 h, cool to ambient temperature, and pour into an aqueous potassium carbonate solution. Extract the resulting mixture with CH_2Cl_2 and wash with saturated aq NaCl. Separate the organic layer, dry over Na_2SO_4, filter, and concentrate. Purify by preparative TLC (5 % methanol in CH_2Cl_2) to obtain the title compound as a yellow solid.

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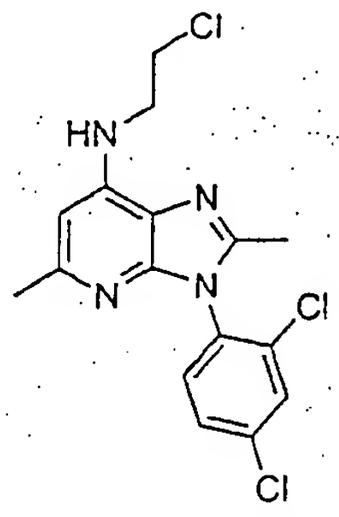
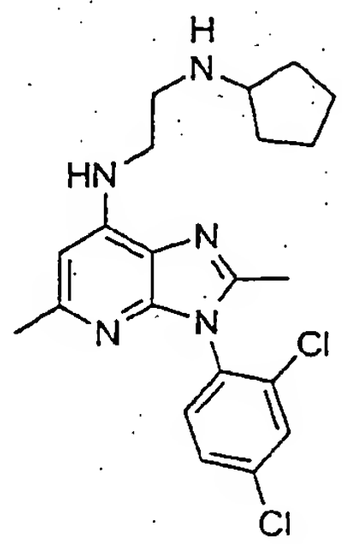
C. [3-(2,4-dichlorophenyl)-2,5-dimethylimidazolo[5,4-b]pyridin-7-yl](2-chloroethyl)amine



Treat a solution of N-[3-(2,4 -dichlorophenyl)-2,5-dimethylimidazolo[5,4-b]pyridin-7-yl]-2-chloroacetamide (1.0 g, 2.6 mmol) in THF (5mL) with borane-methyl sulfide complex (0.8 mL, 7.8mmol). Heat the mixture to reflux for 3 h and quench at ambient temperature with a large excess of MeOH followed by 5 N HCl (2 mL). Re-heat the mixture to reflux for 1 h, then concentrate under reduced pressure. Purify by flash column chromatography (50% EtOAc-hexane) to obtain the title compound as a beige solid.

D. [3-(2,4-dichlorophenyl)-2.5-dimethylimidazolo[5,4-b]pyridin-7-yl][2-(cyclopentylamino)ethyl]amine



Heat a solution of [3-(2,4-dichlorophenyl)-2,5-dimethylimidazolo[5,4-b]pyridin-7-yl](2-chloroethyl)amine (0.08 g, 0.22 mmol), and cyclopentyl amine (0.2 mL g, 0.22 mmol) in dry NMP (3 mL) at 80 ^{0}C for 20 h. Pour the cooled mixture onto water (30 mL) and extract twice with EtOAc (50 mL). Wash the combined extracts with brine (50 mL), dry, and

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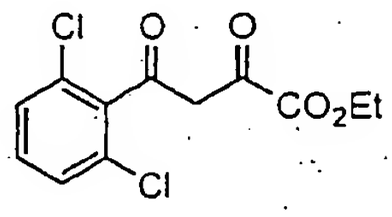
evaporate *in vacuo*. Purify by preparative TLC (10% MeOH in CH_2Cl_2) to obtain the title compound as a yellow oil.

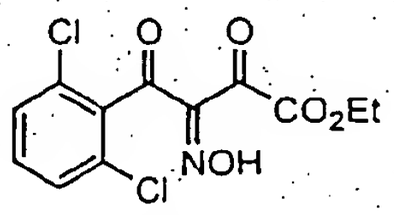
EXAMPLE 8

A. Ethyl 4-(2,6-dichlorophenyl)-2,4-dioxobutanoate



To a solution of 2',6'-dichloroacetophenone (12.5g, 66 mmol) and diethyl oxalate (14.6g, 100mmol) in 450 mL of anhydrous toluene, cautiously add sodium hydride (60% dispersion in mineral oil, 2.8g, 70 mmol). Cautiously heat the reaction mixture to reflux under N_2 for 1 h, cool to ambient temperature and pour onto ice-cold 1M HCl. Separate the layers and extract the aqueous phase with EtOAc (2 x 200 mL). Wash the combined organic extracts with brine, dry over $MgSO_4$ and evaporate to obtain the title compound which is used in the next step without further purification.

B. Ethyl 4-(2,6-dichlorophenyl)-3-(hydroxyimino)-2,4-dioxobutanoate



Slowly bubble N_2O_3 gas (generated by the dropwise addition of concentrated HCl into an aqueous solution of sodium nitrite) into a stirred solution of ethyl 4-(2,6-dichlorophenyl)-2,4-dioxobutanoate (14.4 g, 50 mmol) in EtOH (300 mL) until the reaction is complete (as determined by TLC). Remove the EtOH by evaporation under reduced pressure and partition the residue between EtOAc and water. Dry the organic extract over $MgSO_4$ and evaporate *in vacuo* to obtain the title compound which is used in the next step without further purification.

C. Ethyl 4-amino-5-(2,6-dichlorophenyl)-1-methylpyrazole-3-carboxylate

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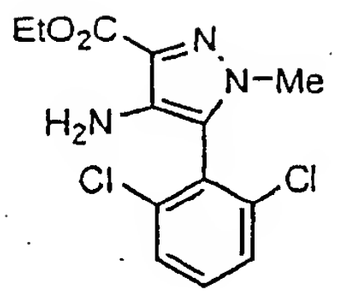
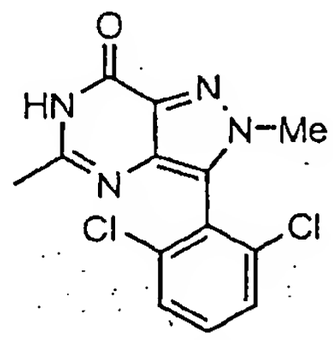


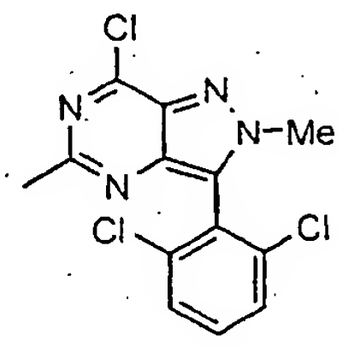
To a solution of ethyl 4-(2,6-dichlorophenyl)-3-(hydroxyimino)-2,4-dioxobutanoate (14 g, 44 mmol) in MeOH (400 mL) at 0°C, add dropwise concentrated HCl (10 mL) followed by methyl hydrazine (2.02g, 44 mmol). Stir the reaction mixture at ambient temperature for 8 h and concentrate *in vacuo*. Partition the residue between EtOAc (400 mL) and saturated aqueous $NaHCO_3$ (150 mL) and separate the layers. Add water (200 mL) to the organic layer, followed by sodium hydrosulfite (150 g) and stir the resulting mixture vigorously for 4 h. Separate the organic phase, wash with water (200 mL), brine (200 mL), dry over $MgSO_4$ and evaporate to obtain the title compound.

D. 3-(2,6-Dichlorophenyl)-2,5-dimethyl-6-hydropyrazolo[4,3-d]pyrimidin-7-one



Saturate a solution of ethyl 4-amino-5-(2,6-dichlorophenyl)-1-methylpyrazole-3-carboxylate (6 g, 20 mmol) in acetonitrile (150 mL) with HCl gas, stir at ambient temperature for 14 h and then concentrate. Partition the residue partition between EtOAc (150 mL) and aqueous $NaHCO_3$ (150 mL) and separate the layers. Wash the organic layer with brine (100 mL), dry over $MgSO_4$ and concentrate. Triturate the residue with Et_2O, and collect the yellow solid by filtration to obtain the title compound.

E. 3-(2,6-Dichlorophenyl)-7-chloro-2,5-dimethylpyrazolo[4,3-d]pyrimidine



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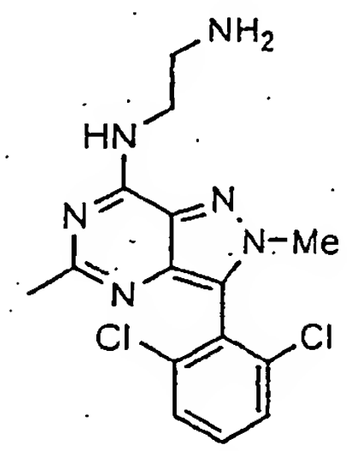
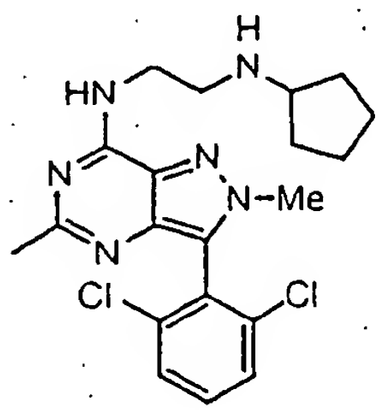
Heat a solution of 3-(2,6-dichlorophenyl)-2,5-dimethyl-6-hydropyrazolo[4,3-d]pyrimidin-7-one (3.09 g, 10 mmol), $POCl_3$ (35 mL) and *N,N*-dimethylaniline (1.44 g, 12 mmol) at 90°C for 8 h. Remove the volatiles by evaporation, re-dissolve the residue in CH_2Cl_2 (100 mL) and wash with aqueous $NaHCO_3$ (2 x 50 mL). Dry the organic layer over $MgSO_4$ and concentrate under reduced pressure. Purify the residue by flash column chromatography (silica, eluent 50% Et_2O in hexane) to obtain the title compound.

F. (2-Aminoethyl)[3-(2,6-dichlorophenyl)-2,5-dimethylpyrazolo[3,4-e]pyrimidin-7-yl]amine



To a stirred solution of 3-(2,6-dichlorophenyl)-7-chloro-2,5-dimethylpyrazolo[4,3-d]pyrimidine (652 mg, 2.0 mmol) in acetonitrile (50 mL) at 50°C, add ethylene diamine (2.4 g, 40 mmol) in one portion. Maintain the reaction at 50°C for 2 h, cool to ambient temperature and remove the volatiles by evaporation. Partition the residue between CH_2Cl_2 (50 mL) and 1N NaOH (50 mL) and extract the aqueous layer with CH_2Cl_2 (2 x 30 mL). Wash the combined organic extracts with water (30 mL), brine (30 mL), dry over $MgSO_4$ and evaporate to obtain the title compound.

G. [3-(2,6-Dichlorophenyl)-2,5-dimethylpyrazolo[3,4-e]pyrimidin-7-yl][2-cyclopentylamino)ethyl]amine



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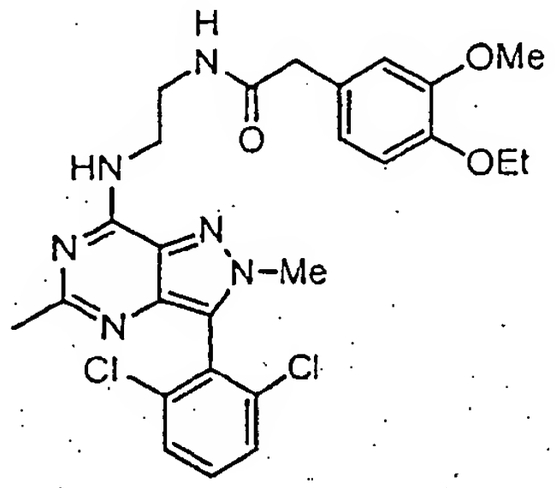
To (2-aminoethyl)[3-(2,6-dichlorophenyl)-2,5-dimethylpyrazolo[3,4-e]pyrimidin-7-yl]amine (140 mg, 0.4 mmol) in dichloroethane (5 mL), add cyclopentanone (34 mg, 0.4 mmol), sodium triacetoxyborohydride (106 mg, 0.5 mmol) and glacial acetic acid (24 mg, 0.4 mmol). Stir the reaction mixture at ambient temperature for 2 h and pour into 1N NaOH (10 mL). Separate the layers and extract the aqueous phase with CH_2Cl_2 (2 x 10 mL). Wash the combined organic extracts with water (10 mL), brine (10 mL), dry over $MgSO_4$ and evaporate *in vacuo*. Purify by preparative TLC (eluent 10% MeOH in chloroform) to obtain the title compound.

EXAMPLE 9

A. *N*-(2-{[3-(2,6-Dichlorophenyl)-2,5-dimethylpyrazolo[3,4-e]pyrimidin-7-yl]amino}-2-(4-ethoxy-3-methoxyphenyl)acetamide



To a stirred solution of (2-aminoethyl)[3-(2,6-dichlorophenyl)-2,5-dimethylpyrazolo[3,4-e]pyrimidin-7-yl]amine (175 mg, 0.5 mmol) in *N*,*N*-dimethylacetamide (5 mL), add 4-methylmorpholine (101 mg, 1.0 mmol), 2-(4-ethoxy-3-methoxyphenyl)acetic acid (115 mg, 0.55 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (331 mg, 0.75 mmol). Stir the reaction mixture at ambient temperature for 14 h and dilute with EtOAc (15 mL). Wash the organic extracts successively with water (10 mL), brine (10 mL), saturated NH_4Cl (10 mL), 2N NaOH (10 mL), brine (10 mL), dry over $MgSO_4$ and evaporate under reduced pressure to obtain the title compound.

B. [3-(2,6-dichlorophenyl)-2,5-dimethylpyrazolo[3,4-e]pyrimidin-7-yl](2-{[2-(4-ethoxy-3-methoxyphenyl)ethyl]amino}ethyl)amine

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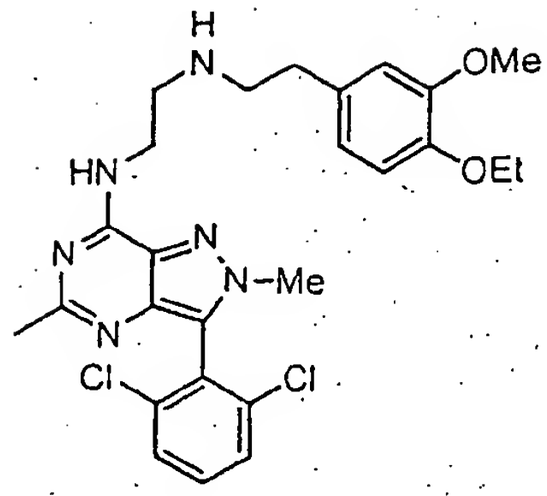
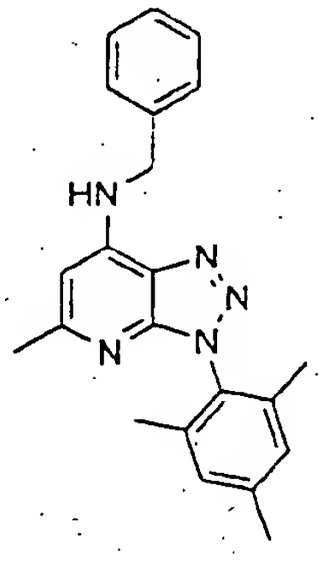


To a stirred solution of *N*-(2-{[3-(2,6-dichlorophenyl)-2,5-dimethylpyrazolo[3,4-e]pyrimidin-7-yl]amino}-2-(4-ethoxy-3-methoxyphenyl)acetamide (175 mg, 0.5 mmol) in THF (5 mL), add borane-dimethylsulfide complex (1M in THF, 0.25 mL, 2.5 mmol). Heat the reaction mixture to reflux for 14 h, cool to ambient temperature and quench by careful addition of MeOH (3 mL). Remove the volatile by evaporation and re-dissolve the residue in MeOH (5 mL). Add HCl in Et_2O (1M, 2 mL) and heat the solution to reflux for 1 h. Remove the volatiles by evaporation under reduced pressure, dissolve the residue in CH_2Cl_2 (20 mL) and wash with saturated $NaHCO_3$ (20 mL) and brine (10 mL). Dry the organic layer over $MgSO_4$ and concentrate *in vacuo*. Purify of the residue by preparative TLC (eluent 20% MeOH in chloroform) to obtain the title compound.

EXAMPLE 10

A. [5-Methyl-3-(2,4,6-trimethylphenyl)(1,2,3-triazolino[5,4-b]pyridin-7-yl)]benzylamine



Treat a solution of 3-amino-6-methyl-4-[benzylamino](2-pyridyl)(2,4,6-trimethylphenyl)amine (1.70 g, 4.91 mmol) in THF (25 mL) with tetrafluoroboric acid (0.86

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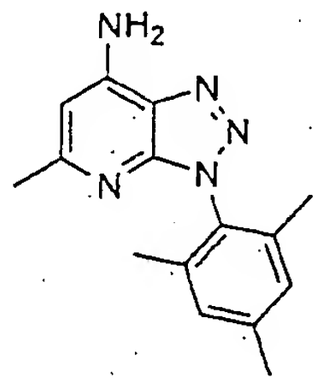
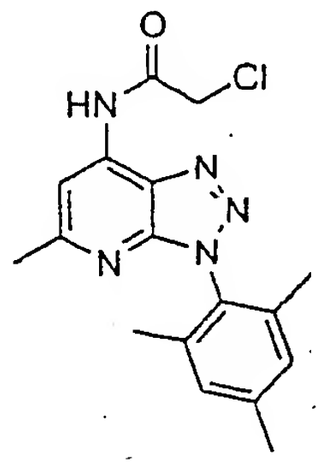
g, 9.81 mmol) at 0°C. Add dropwise isoamyl nitrite (0.86 g, 7.36 mmol) to the reaction mixture, stir at ambient temperature for 30 min, dilute with EtOAc (30 mL), wash with aq $NaHCO_3$ (40 mL), then with saturated aq NaCl (30 mL). Dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by flash column chromatography (50% ethyl acetate-hexane) to obtain the title compound as a solid.

B. 5-Methyl-3-(2,4,6-trimethylphenyl)-1,2,3-triazolino[5,4-b]pyridine-7-ylamine



Add palladium hydroxide (0.5 g) to a solution of [5-methyl-3-(2,4,6-trimethylphenyl)(1,2,3-triazolino[5,4-b]pyridin-7-yl)]benzylamine (0.75g , 2.10 mmol) in acetic acid (10 mL). Hydrogenate the mixture at a pressure of 50 psi for 17 h. Filter the mixture through celite, evaporate to dryness under reduced pressure, dilute with EtOAc and successively wash with aq $NaHCO_3$ and aq NaCl. Dry the organic layer over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by flash column chromatography (3% MeOH in CH_2Cl_2) to obtain the title compound as a solid.

C. 2-Chloro-N-[5-methyl-3-(2,4,6-trimethylphenyl)(1,2,3-triazolino[5,4-b]pyridin-7-yl)]acetamide



Treat a solution of 5-methyl-3-(2,4,6-trimethylphenyl)-1,2,3-triazolino[5,4-b]pyridine-7-ylamine (1.0 g, 3.74 mmol), and N,N-diisopropylethylamine, (0.7 mL, 4.11 mmol) in 1, 2-dichloroethane (10 mL) with chloroacetyl chloride (0.33 mL, 4.11 mmol). Heat the solution

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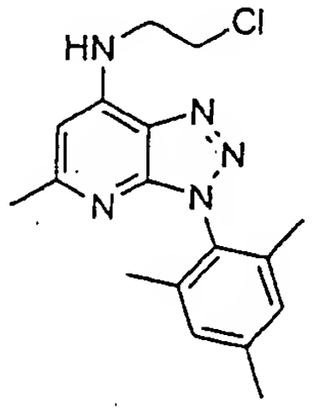
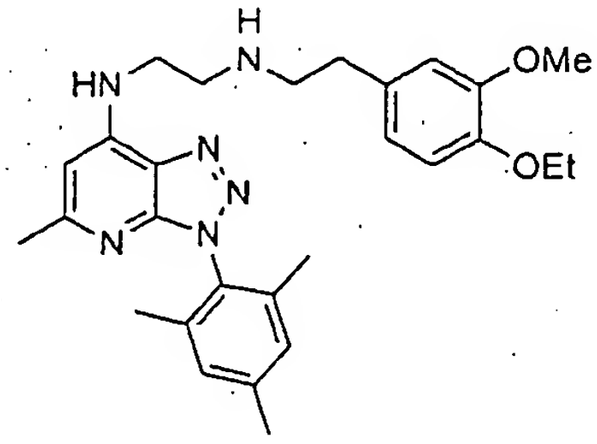
to reflux for 3 h, cool to ambient temperature, and pour into an aqueous potassium carbonate solution. Extract the resulting mixture with CH_2Cl_2 and wash with saturated aq NaCl. Separate the organic layer, dry over Na_2SO_4, filter and concentrate. Purify by flash column chromatography (30% ethyl acetate-hexane)to obtain the title compound as a white crystalline solid.

D. (2-Chloroethyl)[5-methyl-3-(2,4,6-trimethylphenyl)(1,2,3-triazolino[5,4-b]pyridin-7-yl)]amine



Treat a solution of 2-chloro-N-[5-methyl-3-(2,4,6-trimethylphenyl)(1,2,3-triazolino[5,4-b]pyridin-7-yl)]acetamide (0.80 g, 2.33 mmol) in THF (7 mL) with borane-methyl sulfide complex (0.7 mL, 7.0 mmol). Heat the mixture to reflux for 8 h and quench at ambient temperature with a large excess of methanol. Re-heat the mixture to reflux for 1 h, then concentrate under reduced pressure to obtain the title compound as a yellow solid.

E. (2-{[2-(4-Ethoxy-3-methoxyphenyl)ethyl]amino}ethyl)[5-methyl-3-(2,4,6-trimethylphenyl)(1,2,3-triazolino[5,4-b]pyridin-7-yl)]amine



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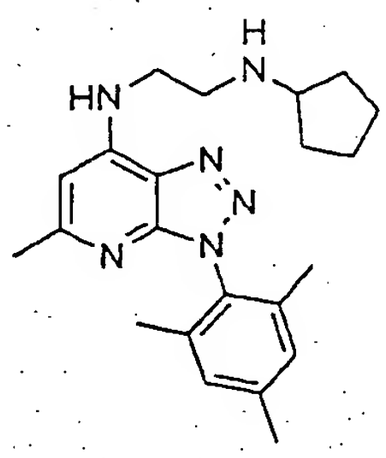
Heat a solution of (2-chloroethyl)[5-methyl-3-(2,4,6-trimethylphenyl)(1,2,3-triazolino[5,4-b]pyridin-7-yl)]amine (0.150 g, 0.45 mmol) and 4-ethoxy-3-methoxy phenethylamine (0.53 g, 2.73 mmol) in dry NMP (3 mL) at 80°C for 14 h. Pour the cooled mixture onto water (50 mL) and extract twice with EtOAc (30 mL). Wash the combined extracts with brine (30 mL), dry, and evaporate *in vacuo*. Purify by flash column chromatography (10% MeOH in CH_2Cl_2-0.1% ammonium hydroxide) to obtain the title compound as a solid.

EXAMPLE 11

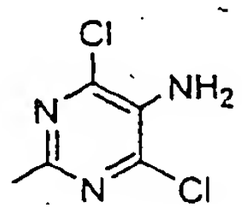
A. [2-(Cyclopentylamino)ethyl][5-methyl-3-(2,4,6-trimethylphenyl)(1,2,3-triazolino[5,4-b]pyridin-7-yl)]amine



Heat a solution of (2-chloroethyl)[5-methyl-3-(2,4,6-trimethylphenyl)(1,2,3-triazolino[5,4-b]pyridin-7-yl)]amine (0.06 g, 0.18 mmol), and cyclopentyl amine (0.53 g, 1.82 mmol) in dry NMP (3 mL) at 80 °C for 14 h. Pour the cooled mixture onto water (30 mL) and extract twice with EtOAc (20 mL). Wash the combined extracts with brine (20 mL), dry, and evaporate *in vacuo*. Purify by flash column chromatography (10% methanol- CH_2Cl_2-0.1% ammonium hydroxide) to obtain the title compound as a solid.

EXAMPLE 12

A. 4,6-Dichloro-2-methyl-5-amino-pyrimidine



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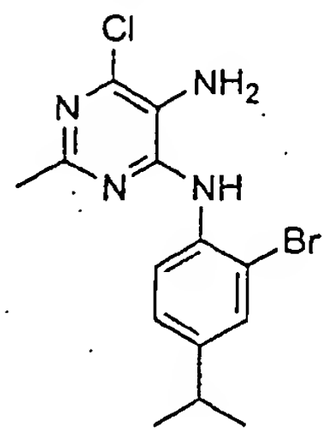
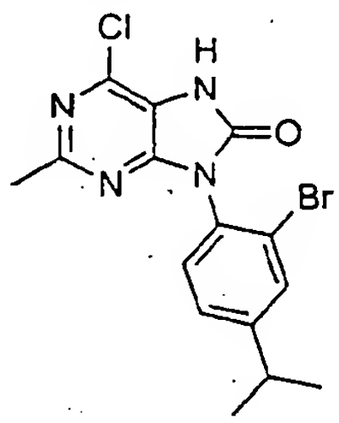
Add iron powder (6.0 g) to a solution of 4,6 dichloro-2-methyl-5-nitro-pyrimidine (6.50 g, 31 mmol) in acetic acid (11 mL) and MeOH (50 mL) . Heat the resulting mixture at 65 ^{0}C for 1 h. After cooling, to ambient temperature, filter the mixture through a pad of celite, and evaporate the filtrate to dryness under reduced pressure. Treat the residue with 1N aq NaOH, and extract with EtOAc . Wash the EtOAc extract with water and saturated aq NaCl, dry over Na_2SO_4, filter, and concentrate *in vacuo* to obtain the title compound as a solid.

B. (5-Amino-6-chloro-2-methylpyrimidin-4-yl)[(2-bromo-4-isopropyl)phenyl]amine



Heat a solution of 4,6-dichloro-2-methyl-5-amino-pyrimidine (2.0 g, 11.2 mmol) and 2-bromo-4-isopropylamine (2.4 g, 11.2 mmol) at 140 ^{0}C for 1 h. After cooling to ambient temperature, dilute the mixture with EtOAc (25 mL), and wash with 1N NaOH (50 mL) and saturated aq NaCl (20 mL). Dry the organic layer over Na_2SO_4, filter, and concentrate under reduced pressure to obtain the title compound as a dark oil which is used without further purification.

C. 9-[(2-Bromo-4-isopropyl)-phenyl]-6-chloro-2-methyl-7-hydropurin-8-one



Treat a solution of (5-amino-6-chloro-2-methylpyrimidin-4-yl)[(2-bromo-4-isopropyl)phenyl]amine (1.0 g, 2.88 mmol) and triethyl amine (0.27 mL, 1.97 mmol) in THF (10 mL) with triphosgene (0.3 g, 0.98 mmol) and stir at ambient temperature for 14 h.

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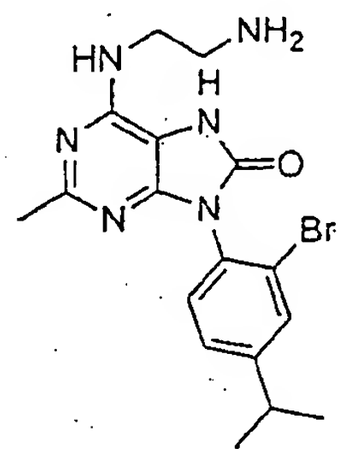
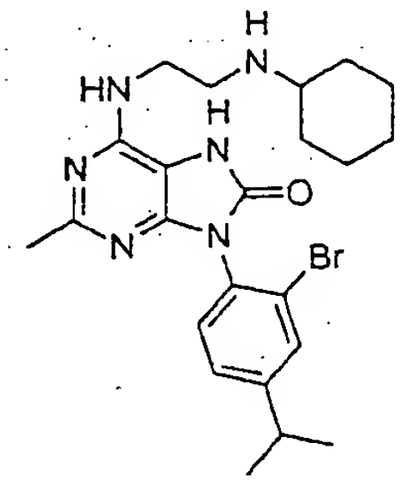
Quench the reaction mixture with water and dilute with EtOAc (20 mL). Separate the organic layer, wash with brine (20 mL), dry over Na_2SO_4, filter, and concentrate under reduced pressure. Purify by flash column chromatography (50% EtOAc- hexane) to obtain the title compound as a dark brown solid.

D. 6-[(2-Aminoethyl)amino]-9-[(2-bromo-4-isopropyl)phenyl]-2-methyl-7-hydropurin-8-one



Heat a solution of 9-[(2-bromo-4-isopropyl)-phenyl]-6-chloro-2-methyl-7-hydropurin-8-one (0.34 g, 0.89 mmol), and ethylenediamine (0.32 g, 5.37 mmol) in dry NMP (2 mL) at 85^0 C for 14 h. Pour the cooled mixture onto water (50 mL) and extract twice with EtOAc (30 mL). Wash the combined extracts with brine (30 mL), dry, and evaporate *in vacuo* to obtain the title compound which is used without further purification.

E. 9-[(2-Bromo-4-isopropyl)phenyl]-6-{[2-(cyclohexylamino)ethyl]amino}-2-methyl-7-hydropurin-8-one



Treat a solution of 6-[(2-aminoethyl)amino]-9-[(2-bromo-4-isopropyl)phenyl]-2-methyl-7-hydropurin-8-one (0.100 g, 0.248 mmol), cyclohexanone (0.03 mL, 0.248 mmol) and acetic acid (0.01 mL, 0.248 mmol) in dry dichloroethane (3 mL) with sodium triacetoxyborohydride (0.07g, 0.347 mmol) and stir at ambient temperature for 10 h. Dilute the resulting mixture

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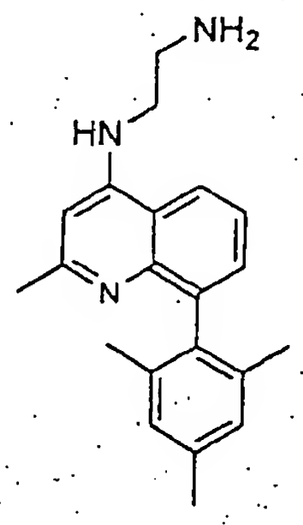
with CH_2Cl_2 (20 mL) and wash with saturated aq NaCl (50 mL). Dry the organic phase over Na_2SO_4, filter, and concentrate under reduced pressure. Purify by preparative TLC (10 % methanol in CH_2Cl_2 with 0.5 % ammonium hydroxide) to obtain the title compound as a yellow solid.

EXAMPLE 13

A. (2-Aminoethyl)[2-methyl-8-(2,4,6-trimethylphenyl)(4-quinolyl)]amine



In a sealed tube, heat 4-bromo-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline (100 mg, 0.29 mmol) at 140°C in a mixture of ethylene glycol (1 mL) and ethylene diamine (0.3 mL). After 4 h, cool the reaction mixture and partition between saturated aqueous $NaHCO_3$ and chloroform. Dry the combined organic extracts on Na_2SO_4 and concentrate under reduced pressure to obtain the title compound as a yellow glass: +APcI MS $(M+1)^+$ 320; ^1H NMR (methanol-d_4) δ: 7.78 (dd, 1H), 7.39 (t, 1H), 7.34 (dd, 1H), 6.95 (s, 2H), 6.31 (s, 1H), 3.34 (t, 2H), 3.11 (t, 2H), 2.43 (s, 3H), 2.34 (s, 3H), 1.89 (s, 6H).

B. [2-Methyl-8-(2,4,6-trimethylphenyl)(4-quinolyl)][2-(2-1,2,3,4-tetrahydronaphthylamino)ethyl]amine hydrochloride

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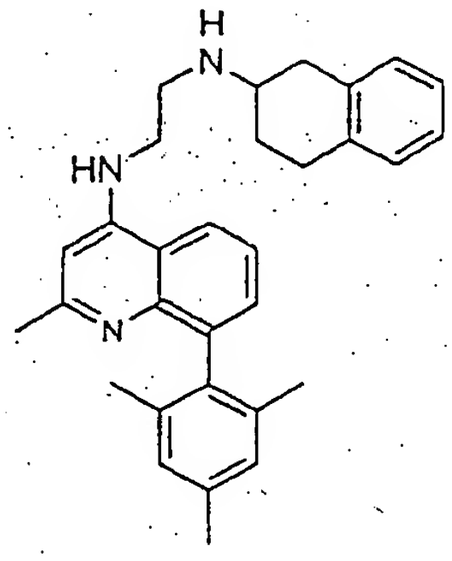
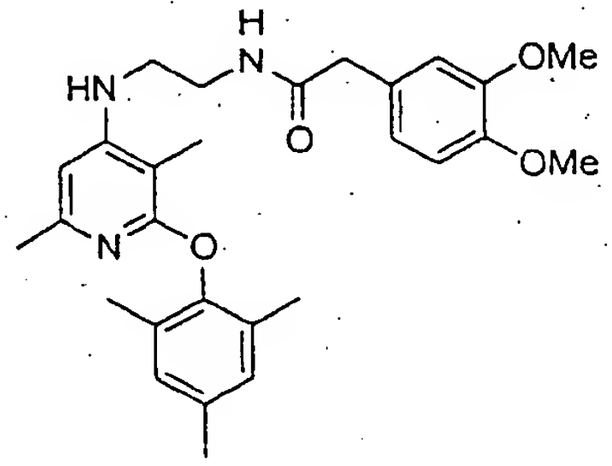


To a stirred solution of (2-aminoethyl)[2-methyl-8-(2,4,6-trimethylphenyl)(4-quinolyl)]amine (21 mg, 0.066 mmol) and 1,2,3,4-tetrahydro-2-naphthalenone (42 mg, 0.29 mmol) in MeOH (1 mL)/acetic acid (0.01 mL), add sodium cyanoborohydride (4 mg, 0.3 mmol). After stirring 4 h, concentrate the reaction mixture under reduced pressure and partition between saturated aqueous $NaHCO_3$ and chloroform. Dry the combined organic extracts on Na_2SO_4, concentrate under reduced pressure, and purify by column chromatography on silica gel (eluent: 32:1 EtOAc/triethylamine) to obtain the title compound as a colorless glass. Treat a methanolic solution of the product with concentrated aqueous hydrochloric acid to generate the hydrochloride salt. Concentrate the solution under reduced pressure and triturate the residue in Et_2O to obtain the title compound as a colorless solid: +APcI MS $(M+1)^+$ 450; ^1H NMR (methanol-d_4) δ: 8.52 (dd, 1H), 7.78 (t, 1H), 7.62 (dd, 1H), 7.15-7.00 (m, 7H), 4.06 (t, 2H), 2.66 (s, 3H), 2.38 (s, 3H), 1.87 (s, 6H).

EXAMPLE 14

A. 2-(3,4-Dimethoxyphenyl)-N-(2-{[3,6-dimethyl-2-(2,4,6-trimethylphenoxy)(4-pyridyl)]amino}ethyl)acetamide



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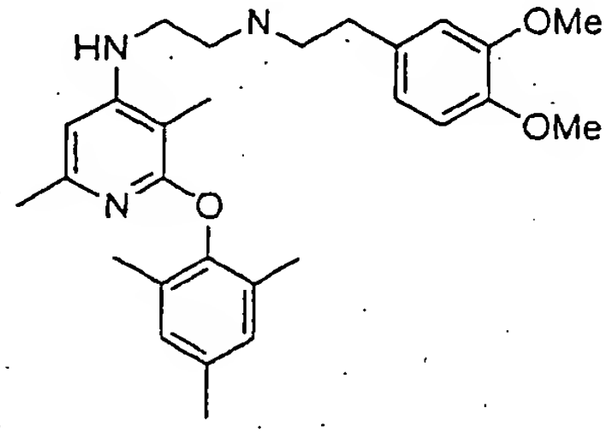
Stir a solution of [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-4-pyridyl][2-(methylamino)ethyl]amine (68 mg, 0.23 mmol), 3,4-dimethoxyphenylacetic acid (59 mg, 0.3 mmol), EDC (59 mg, 0.3 mmol) and HOBT (41 mg, 0.3 mmol) in DMF (1.0 mL) for 12 h. Dilute the reaction mixture with EtOAc (10 mL) and wash with saturated aq $NaHCO_3$ (2 x 10 mL) and saturated aq brine (2 x 10 mL), dry and concentrate *in vacuo* to obtain the title compound as an oily residue. M+1: 478.

B. (2-{[2-(3,4-Dimethoxyphenyl)ethyl]amino}ethyl)[3,6-dimethyl-2-(2,4,6-trimethylphenoxy) (4-pyridyl)]amine



Add BH_3 in THF (1 M solution, 0.3 mmol, 0.3 mL) to a solution of the crude 2-(3,4-dimethoxyphenyl)-N-(2-{[3,6-dimethyl-2-(2,4,6-trimethylphenoxy)(4-pyridyl)]amino}ethyl) acetamide in THF (2.0 mL) at ambient temperature. Heat the reaction mixture under reflux for 15 h, dilute with a solution of 10% aq HCl/MeOH (1:1, 2 mL) and heat again under reflux (1 h). Dilute the reaction mixture with $CHCl_3$ (10 mL), wash with saturated aq $NaHCO_3$ (1 x 5 mL), dry and concentrate *in vacuo*. Chromatograph the crude residue on SiO_2-gel using a gradient of 100% EtOAc to 10% Et_2NH/EtOAc to obtain the title compound as a colorless oil. Immediately dissolve the product in Et_2O (1 mL), treat with excess 4 M HCl/dioxane and concentrate *in vacuo* to obtain the hydrochloride salt of the title compound as a colorless solid. ^1H NMR (d_4-MeOH, Unity 400): d 6.99 – 6.77 (6H, m), 3.81 (3H, s), 3.78 (3H, s), 3.62 (2H, m), 2.98 (2 H, t), 2.39 (3H, s), 2.29 (3H, s), 2.16 (3H, s), 2.07 (6H, s). M+1: 464.

EXAMPLE 15

A. (2-Aminoethyl){2-methyl-6-[(2,4,6-trimethylphenyl)amino]pyrimidin-4-yl}amine

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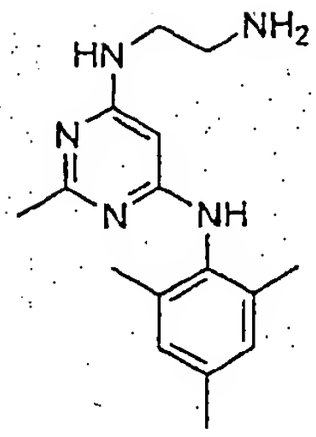
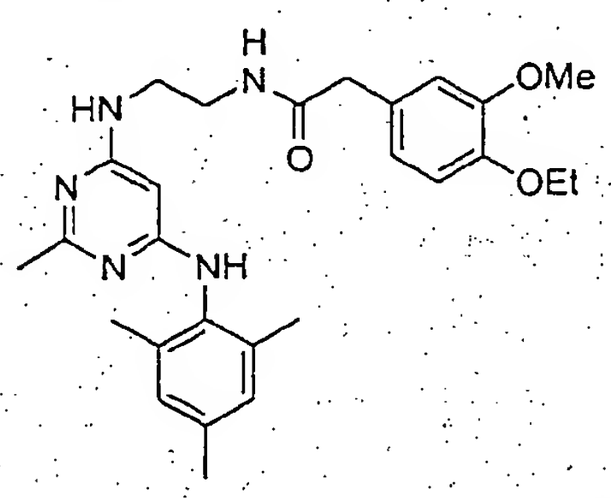


Heat a solution of 6-chloro-2 methyl-pyrimidin-4-yl)-(2,4,6-trimethyl-phenyl)-amine (0.50 g, 1.91 mmol), and ethylenediamine (1.28 mL, 19.10 mmol) in dry NMP (5 mL) at 100 ^{0}C for 14 h. Pour the cooled mixture onto water (50 mL) and extract twice with EtOAc (30 mL). Wash the combined extracts with brine (30 mL), dry, and evaporate *in vacuo*. Purify by preparative TLC (10 % methanol- CH_2Cl_2- 0.5 % ammonium hydroxide) to obtain the title compound.

B. 2-(4-Ethoxy-3-methoxy-phenyl)-N-{2-[2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidin-4-ylamino]ethyl}-acetamide



To a solution of (2-aminoethyl){2-methyl-6-[(2,4,6-trimethylphenyl)amino]pyrimidin-4-yl}amine (0.36g, 1.26 mmol), 4-ethoxy-3-methoxyphenethylamine (0.26g, 1.26 mmol)) and N,N diisopropylethyl amine (0.24 ml, 1.38 mmol in CH_2Cl_2 (5 mL), add benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (0.61g, 1.38 mmol) and stir at ambient temperature for 14 h. Dilute the resulting mixture with CH_2Cl_2 (20 mL), and wash with water (20 mL) and saturated aq NaCl (20 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by preparative TLC (7 % methanol- CH_2Cl_2) to obtain the title compound.

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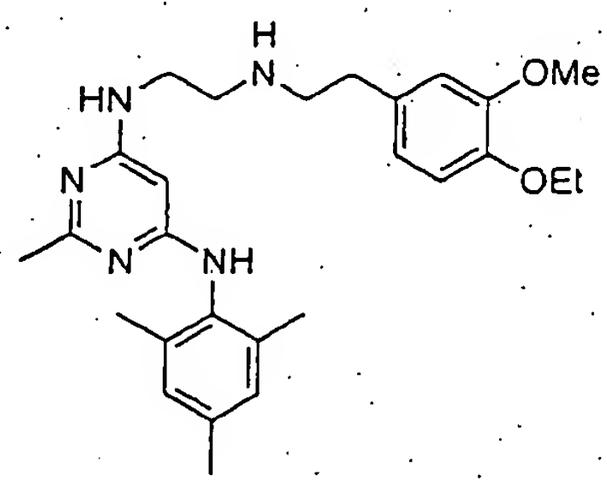
C. (2-{[2-(4-Ethoxy-3-methoxyphenyl)ethyl]amino}ethyl){2-methyl-6-[(2,4,6-trimethylphenyl)amino]pyrimidin-4-yl}amine



Heat a solution of 2-(4-ethoxy-3-methoxy-phenyl)-N-{2-[2-methyl-6-(2,4,6-trimethyl-phenylamino)-pyrimidin-4-ylamino]ethyl}-acetamide (0.324 g, 0.68 mmol) in THF (10 mL) with $AlH_3.NMe_2Et$ (14 mL, 6.78 mmol) to reflux for 14 h. Cool the resulting mixture to ambient temperature, quench with $Na_2CO_3.10H_20$ (1.0 g) and stir at ambient temperature for 15 min. Filter the solution through Celite and wash with several portions of CH_2Cl_2. Concentrate the filtrate *in vacuo* to dryness and purify by preparative TLC (10 % MeOH in CH_2Cl_2) to obtain the title compound.

The preparation of the compounds of the present invention by the above-mentioned methods is illustrated further by the following examples, delineated in the TABLE which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. Commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, cPr is cyclopropyl, Bu is butyl, iBu is isobutyl (CH_2-$CHMe_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, Bn is benzyl (CH_2Ph), Ac is acetyl (CH_3-(C=O)), tBOC is tert-butyloxycarbonyl (tBuO-(C=O)). EX means example.

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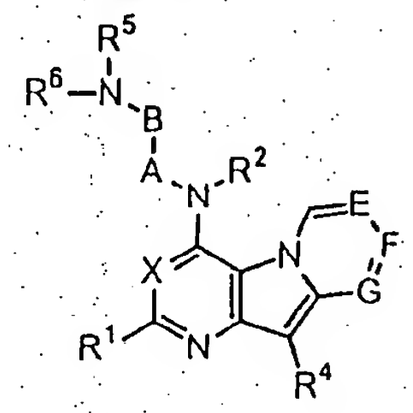
Tables of Examples

TABLE 1.



EX	X	R1	R2	E	F	G	R4	A-B-N[R^6]-R^5
16.	CH	Me	H	CH	CH	CH	2,6-diMe-4-OMe-Ph	(CH2)2-NH-(CH2)2-(3,4-diOMe-Ph)
17.	CH	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3,4-diOMe-Ph)
18.	CH	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(4-OCF3-Ph)
19.	CH	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-cPent
20.	CH	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-cHex
21.	CH	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
22.	CH	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
23.	CH	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
24.	CH	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cPent
25.	CH	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cHex
26.	CH	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4-OH-cHex)

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27.	CH	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
28.	CH	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
29.	CH	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
30.	N	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-N(cPent)2
31.	N	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3,4-diOMe-Ph)
32.	N	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
33.	N	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-cHex
34.	N	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
35.	N	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
36.	N	Me	H	CH	CH	CH	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
37.	N	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cPent
38.	N	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cHex
39.	N	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4-OH-cHex)
40.	N	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
41.	N	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
42.	N	Me	H	CH	CH	CH	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
43.	N	Me	H	CH	CH	CH	2,6-diCl-4-OEt-Ph	(CH2)2-NH-cPent
44.	N	Me	H	CH	CH	CH	2,6-diCl-4-OEt-Ph	(CH2)2-NH-cHex
45.	N	Me	H	CH	CH	CH	2,6-diCl-4-OEt-Ph	(CH2)2-NH-(4-OH-cHex)
46.	N	Me	H	CH	CH	CH	2,6-diCl-4-OEt-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
47.	N	Me	H	CH	CH	CH	2,6-diCl-4-OEt-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
48.	N	Me	H	CH	CH	CH	2,6-diCl-4-OEt-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)

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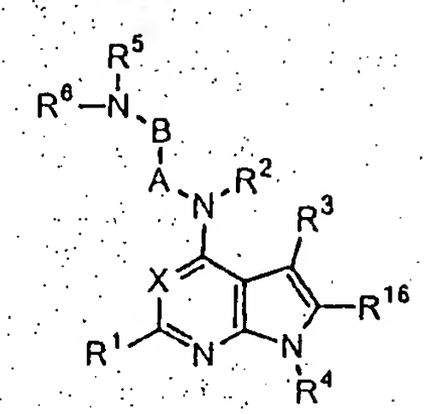
TABLE 2



EX	X	R1	R2	R3	R16	R4
49.	CH	Me	H	Me	H	2,4,6-triMe-Ph
50.	CH	Me	H	Me	H	2,4,6-triMe-Ph
51.	CH	Me	H	Me	H	2,4,6-triMe-Ph
52.	CH	Me	H	Me	H	2,4,6-triMe-Ph
53.	CH	Me	H	Me	H	2,4,6-triMe-Ph
54.	CH	Me	H	Me	H	2,4,6-triMe-Ph
55.	CH	Me	H	Me	H	2,4,6-triMe-Ph
56.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
57.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
58.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
59.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
60.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
61.	CH	Me	H	Me	H	2,6-diCl-4-OEt-Ph

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62.	CH	Me	H	Me	H	2,6-diCl-4-OEt-Ph
63.	CH	Me	H	Me	H	2,6-diCl-4-OEt-Ph
64.	CH	Me	H	Me	H	2,6-diCl-4-OEt-Ph
65.	CH	Me	H	Me	H	2,6-diCl-4-OEt-Ph
66.	N	Me	H	Me	H	2,4,-diMe-4-Br-Ph
67.	N	Me	H	Me	Me	2,4,6-triMe-Ph
68.	N	Me	H	Me	H	2,4,6-triMe-Ph
69.	N	Me	H	Me	Me	2,4,6-triMe-Ph
70.	N	Me	H	Me	H	2,4,6-triMe-Ph
71.	N	Me	H	Me	H	2,4,6-triMe-Ph

SDOCID: <WO___0123389A2_I_>

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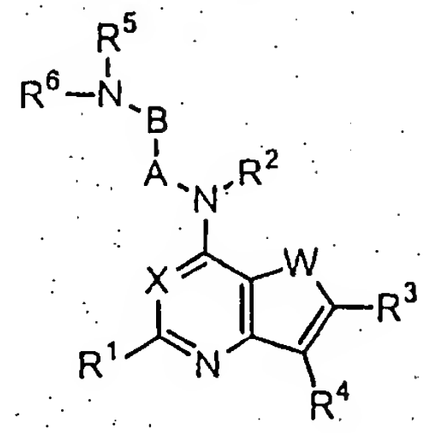
TABLE 3



2

3

	EX	X	W	R1	R2	R3	R4	A-B-N[R^6]-R^5
	72.	N	NMe	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(4-OMe-Ph)
	73.	N	NMe	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	74.	N	NMe	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-cHex
	75.	N	NMe	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	76.	N	NMe	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	77.	N	NMe	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)

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	78.	N	NMe	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
	79.	N	S	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(4-OMe-Ph)
	80.	N	S	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	81.	N	S	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-cHex
	82.	N	S	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	83.	N	S	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	84.	N	S	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	85.	N	S	Me	H	H	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)

INSDOCID: <WO___0123389A2_I_>

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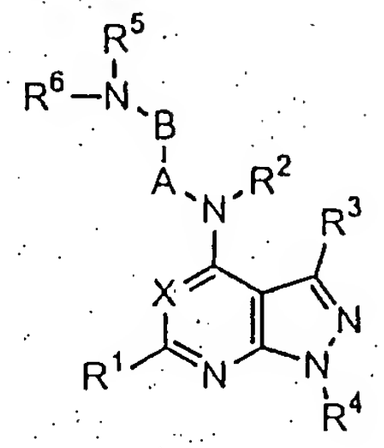
TABLE 4



2

#	EX	X	R1	R2	R3	R4
	86.	N	Me	H	H	2,4,6-triMe-Ph
	87.	N	Me	H	H	2,4,6-triMe-Ph
	88.	N	Me	H	H	2,4,6-triMe-Ph
	89.	N	Me	H	H	2,4,6-triMe-Ph
	90.	N	Me	H	H	2,4,6-triMe-Ph
	91.	N	Me	H	H	2,4,6-triMe-Ph
	92.	N	Me	H	H	2,4,6-triMe-Ph

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3DOCID: <WO__0123389A2_1_>

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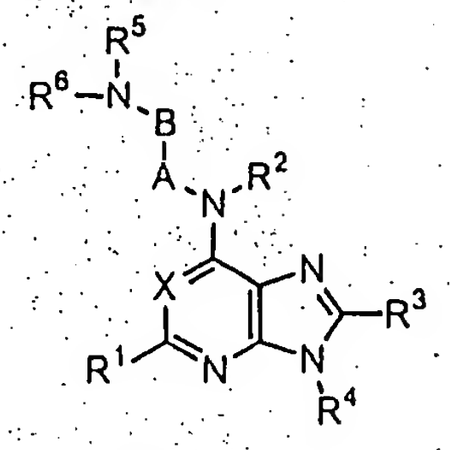
TABLE 5



2

3

R^1 is methyl

	EX	X	R2	R3	R4	A-B-N[R^6]-R^5
	93.	CH	H	Me	2,4,-diCl-Ph	(CH2)2-NH-(CH2)2-(2-OiPr-5-pyridyl)
	94.	CH	H	Me	2,4,-diCl-Ph	(CH2)2-NH-cHex
	95.	CH	H	Me	2,4-diCl-Ph	(CH2)2-NH-(CH2)2-((3-OMe-4-OiPr)-Ph)
	96.	CH	H	Me	2,4,6-triMe-3-Py	(CH2)2-NH-(CH2)2-(3-OMe-4-iPrO-Ph)
	97.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cBu
	98.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	99.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	100.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	101.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	102.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(2-OiPr-5-pyridyl)
	103.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
	104.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-iPrO-Ph)

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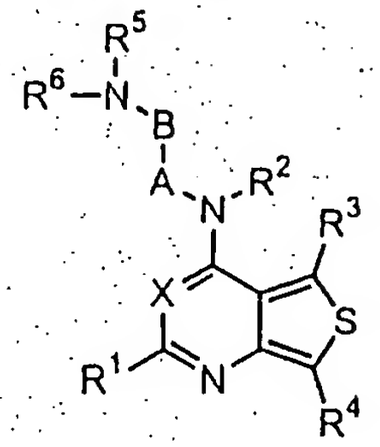
	105.	CH	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cPent
	106.	CH	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cHex
	107.	CH	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4-OH-cHex)
	108.	CH	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	109.	CH	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	110.	CH	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
	111.	N	H	Me	2-Br-4-iPr-Ph	(CH2)2-NH-cPent
	112.	N	H	Cl	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	113.	N	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	114.	N	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cHex
	115.	N	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	116.	N	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	117.	N	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	118.	N	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
	119.	N	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-iPrO-Ph)
	120.	N	H	Cl	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	121.	N	H	Cl	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
	122.	N	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cPent
	123.	N	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cHex
	124.	N	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4-OH-cHex)
	125.	N	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	126.	N	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)

SDOCID: <WO___0123389A2_I_>

TABLE 6

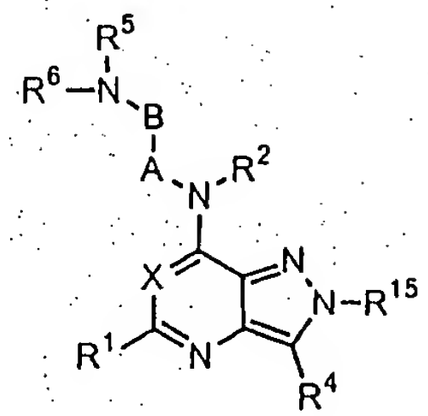


R^1 is mrthyl

	EX	X1	R2	R3	R4	A-B-N[R^6]-R^5
	127.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	128.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cHex
	129.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	130.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	131.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	132.	CH	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)

\SDOCID: <WO___0123389A2_I_>

TABLE 7



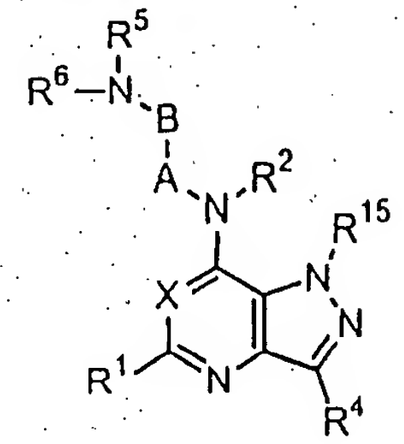
EX	X	R1	R2	R15
133.	N	Me	H	Me
134.	N	Me	H	Me
135.	N	Me	H	Me
136.	N	Me	H	Me
137.	N	Me	H	Me
138.	N	Me	H	Me
139.	N	Me	H	Me
140.	N	Me	H	Me
141.	N	Me	H	Me
142.	N	Me	H	Me
143.	N	Me	H	Me
144.	N	Me	H	Me

145.	N	Me	H	Me
146.	N	Me	H	Me
147.	N	Me	H	Me
148.	N	Me	H	Me
149.	N	Me	H	Me

SDOCID: <WO__0123389A2_I_>

SDOCID: <WO___0123389A2_I_>

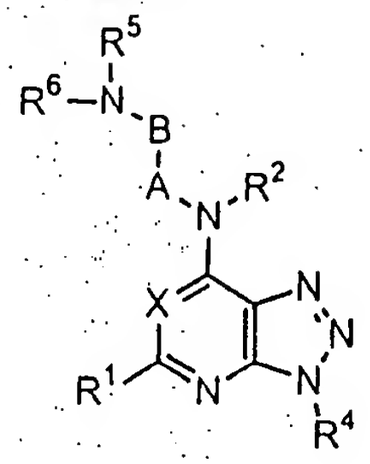
TABLE 8



	EX	X	R1	R2	R15	R4	A-B-N[R^6]-R^5	
	150.	N	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent	
	151.	N	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cHex	
	152.	N	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)	
	153.	N	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	
	154.	N	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	
	155.	N	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)	
	156.	N	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cPent	
	157.	N	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cHex	
	158.	N	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4-OH-cHex)	
	159.	N	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)	
	160.	N	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)	
	161.	N	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)	

SDOCID: <WO__0123389A2_I_>

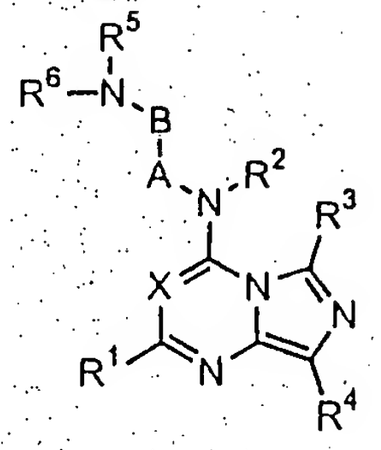
TABLE 9



EX	X	R1	R2	R4	A-B-N[R^6]-R^5
162.	CH	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-iPrO-Ph)
163.	CH	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-cBu
164.	CH	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-cHex
165.	CH	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
166.	CH	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
167.	CH	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
168.	CH	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
169.	CH	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cPent
170.	CH	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cHex
171.	CH	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4-OH-cHex)
172.	CH	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
173.	CH	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
174.	CH	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)

NSDOCID: <WO___0123389A2_I_>

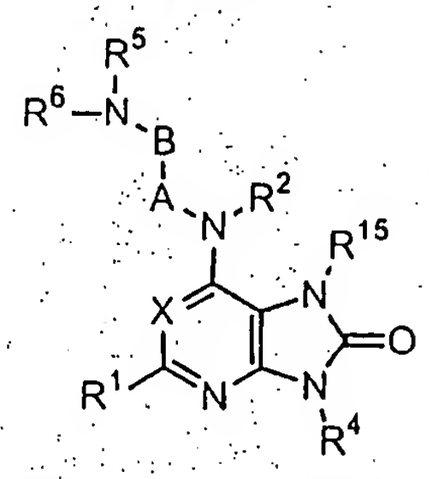
TABLE 10



EX	x	R1	R2	R3	R4
175.	CH	Me	H	Me	2,4,6-triMe-Ph
176.	CH	Me	H	Me	2,4,6-triMe-Ph
177.	CH	Me	H	Me	2,4,6-triMe-Ph
178.	CH	Me	H	Me	2,4,6-triMe-Ph
179.	CH	Me	H	Me	2,4,6-triMe-Ph
180.	CH	Me	H	Me	2,4,6-triMe-Ph

3DOCID: <WO___0123389A2_I_>

TABLE 11



	EX	X	R1	R2	R15
	181.	CH	CH	H	Me
	182.	CH	CH	H	Me
	183.	CH	CH	H	Me
	184.	CH	CH	H	Me
	185.	CH	CH	H	Me
	186.	N	CH	H	Me
	187.	N	CH	H	Me
	188.	N	CH	H	Me
	189.	N	CH	H	Me
	190.	N	CH	H	Me
	191.	N	CH	H	Me

SDOCID: <WO___0123389A2_I_>

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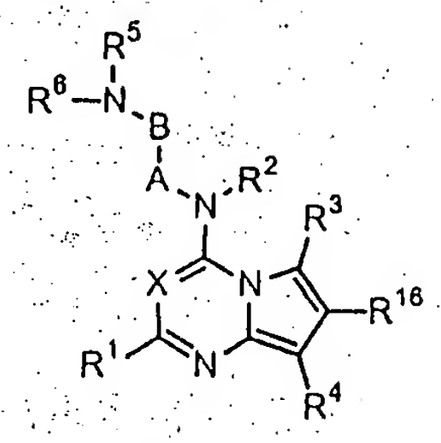
TABLE 12



	EX	X	R1	R2	R3	R16	R4	A-B-N[R^6]-R^5
	192.	CH	Me	H	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	193.	CH	Me	H	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-cHex
	194.	CH	Me	H	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	195.	CH	Me	H	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	196.	CH	Me	H	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	197.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cPent
	198.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cHex
	199.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(4-OH-cHex)
	200.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	201.	CH	Me	H	Me	H	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	202.	N	Me	H	Me	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(4-OMe-Ph)
	203.	N	Me	H	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	204.	N	Me	H	Me	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent

	205.	N	Me	H	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-Et
	206.	N	Me	H	Me	H	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	207.	N	Me	H	Me	Me	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)

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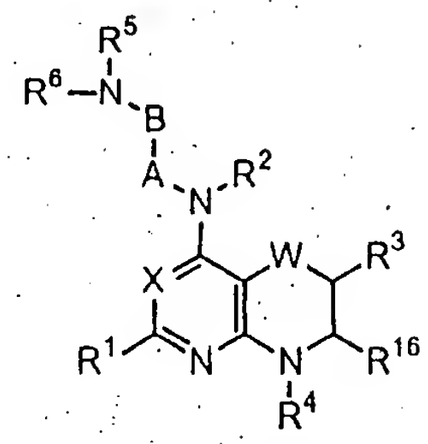
TABLE 13



	EX	X	W	R1	R2	R3	R16	R4
	208.	CH	NH	Me	H	Me	H	2,4,6-triMe-Ph
	209.	CH	NH	Me	H	Me	H	2,4,6-triMe-Ph
	210.	CH	NH	Me	H	Me	H	2,4,6-triMe-Ph
	211.	CH	NH	Me	H	Me	H	2,4,6-triMe-Ph
	212.	CH	NH	Me	H	Me	H	2,4,6-triMe-Ph
	213.	CH	NH	Me	H	Me	H	2,4,6-triMe-Ph
	214.	CH	NH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
	215.	CH	NH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
	216.	CH	NH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
	217.	CH	NH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
	218.	CH	NH	Me	H	Me	H	2,6-diCl-4-OMe-Ph
	219.	N	NH	Me	H	Me	H	2,4,6-triMe-Ph

	220.	N	NH	Me	H	Me	H	2,4,6-triMe-Ph
	221.	N	NH	Me	H	Me	H	2,4,6-triMe-Ph
	222.	N	NH	Me	H	Me	H	2,4,6-triMe-Ph
	223.	N	NH	Me	H	Me	H	2,4,6-triMe-Ph
	224.	N	NH	Me	H	Me	H	2,4,6-triMe-Ph

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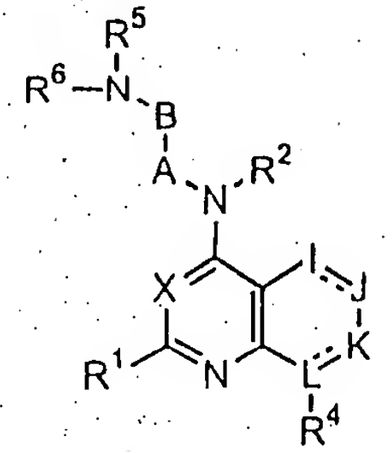
TABLE 14



	EX	X	R1	R2	I	J	K
	225.	CH	Me	H	CH	CH	CH
	226.	CH	Me	H	CH	CH	CH
	227.	CH	Me	H	CH	CH	CH
	228.	CH	Me	H	CH	CH	CH
	229.	CH	Me	H	CH	CH	CH
	230.	CH	Me	H	CH	CH	CH
	231.	CH	Me	H	CH	CH	CH

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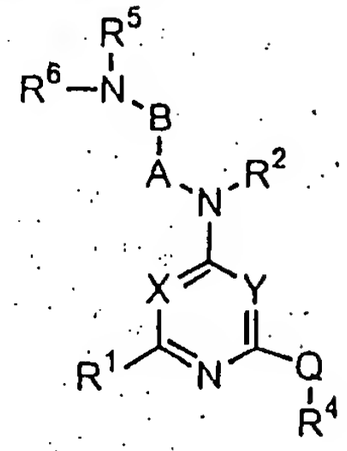
TABLE 15



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	EX	X	Y	R1	R2	Q	R4	A-B-N[R^6]-R^5
	232.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)2-NcPent-(tetrahydropyran-4-yl)
	233.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	234.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)2-NH-cPent.
	235.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)3-NH-(1-Ac-piperidin-4-yl)
	236.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)3-NH-(1,2,3,4-tetrahydro-naphthalen-2-yl)
	237.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)4-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	238.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)4-NH-(1-Ac-piperidin-4-yl)
	239.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)4-NH-(1,2,3,4-tetrahydro-naphthalen-2-yl)
	240.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	CH2-CHMe-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	241.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)2-NH-cHex
	242.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	243.	CH	CMe	Me	H	O	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	244.	N	CH	Me	H	NH	2,4,6-triMe-Ph	(CH2)2-NH-cPent

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	245.	N	CH	Me	H	NH	2,4,6-triMe-Ph	(CH2)2-NH-cHex
	246.	N	CH	Me	H	NH	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	247.	N	CH	Me	H	NH	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	248.	N	CH	Me	H	NH	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	249.	CH	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	250.	CH	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-cHex
	251.	CH	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	252.	CH	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	253.	CH	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	254.	CH	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)
	255	N	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-cPent
	256	N	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-cHex
	257	N	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-(4-OH-cHex)
	258	N	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-(tetrahydropyran-4-yl)
	259	N	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl)
	260.	N	N	Me	H	NEt	2,4,6-triMe-Ph	(CH2)2-NH-(CH2)2-(3-OMe-4-EtO-Ph)

1

Example 261 Characterization of NPY receptor interactions and in vivo function

A. Assay for Human NPY_1 Receptor Binding Activity: Compounds are assayed for activity using the following method: A cDNA encoding human NPY1 (SEQ ID NO:1) is ligated in the appropriate orientation for expression into the commercial expression vector pBacPAK9 (Clontech, Palo Alto, CA) for expression in SF9 cells. Each Baculoviral expression vector is co-transfected along with BACULOGOLD DNA (BD PharMingen, San Diego, CA) into S*f*9 cells. The S*f*9 cell culture supernatant is harvested three days post-transfection. The recombinant virus-containing supernatant is serially diluted in Hink's TNM-FH insect medium (JRH Biosciences, Kansas City) supplemented Grace's salts and with 4.1mM L-Gln, 3.3 g/L LAH, 3.3 g/L ultrafiltered yeastolate and 10% heat-inactivated fetal bovine serum (hereinafter "insect medium") and plaque assayed for recombinant plaques. After four days, recombinant plaques are selected and harvested into 1 ml of insect medium for amplification. Each 1 ml volume of recombinant baculovirus (at passage 0) is used to infect a separate T25 flask containing 2 x 10^6 S*f*9 cells in 5 mL of insect medium. After five days of incubation at 27°C, supernatant medium is harvested from each of the T25 infections for use as passage 1 inoculum. Recombinant baculoviral clones are then subjected to a second round of amplification, using 1 ml of passage 1 stock to infect 1 x 10^8 cells in 100 ml of insect medium divided into 2 T175 flasks. Forty-eight h post infection, passage 2 medium is harvested from each 100ml prep and plaque assayed for titer. The cell pellets from the second round of amplification are assayed for affinity binding of radiolabeled ligand (see below) to verify recombinant receptor expression. A third round of amplification is then initiated using an M.O.I. of 0.1 to infect a liter of S*f*9 cells. Forty h post-infection the supernatant medium is harvested to yield passage 3 baculoviral stock and the cell pellet assayed for affinity binding. Titer of the passage 3 baculoviral stock is determined by plaque assay and an M.O.I. and Incubation Time Course experiment is carried out to determine conditions for optimal receptor expression.

Log-phase S*f*9 cells are infected with stocks of recombinant baculovirus encoding the proteins of interest (e.g., human NPY1 and three g-proteins), followed by culturing in insect medium at 27°C. 72 h post-infection, a sample of cell suspension is analyzed for viability by

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trypan blue dye exclusion, and the remaining *Sf*9 cells are harvested via centrifugation (3000 rpm/ 10 minutes/ 4°C).

B. Preparation of purified membranes: *Sf*9 cell pellets are resuspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 □g/ml leupeptin, 2 □g/ml Aprotinin, 200 □M PMSF, and 2.5 mM EDTA, pH 7.4) and homogenized using a POLYTRON homogenizer (setting 5 for 30 seconds). The homogenate is centrifuged (536 x g/ 10 minutes/ 4°C) to pellet the nuclei. The supernatant containing isolated membranes is decanted to a clean centrifuge tube, centrifuged (48,000 X g/ 30 minutes, 4°C) and resuspended in 30 ml, or preferably 20 ml of homogenization buffer. This centrifugation and resuspension step is repeated twice. The final pellet is resuspended in ice cold Dulbecco's PBS containing 5 mM EDTA and stored in frozen aliquots until needed at -80°C. The protein concentration of the resulting membrane preparation is measured using the Bradford protein assay (Bio-Rad Laboratories, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 50-100 mg of total membrane protein.

CO-infection for GTPγ^{35}S binding assay: Four baculoviral expression vector stocks are used to infect a culture of *Sf*9 cells with an MOI of 1:1:1:1. These four consisted of one vector encoding the human NPY1 receptor and a different commercially obtained baculoviral expression vector stock encoding each of the three subunits of a heterotrimeric G-protein, in particular, the G-protein-encoding virus stocks are obtained from BIOSIGNAL Inc., Montreal, and are 1) a Gα G-protein subunit-encoding virus stock (either the rat $G\alpha_{i2}$ G-protein-encoding virus stock BIOSIGNAL #V5J008 or the rat $G\alpha_o$ G-protein-encoding virus stock BIOSIGNAL #V5H010), 2) a bovine β1 G-protein-encoding virus stock (BIOSIGNAL #V5H012), and 3) a human γ2 G-protein-encoding virus stock (BIOSIGNAL #V6B003). Agonist-stimulated GTPγ^{35}S binding on purified membranes is assessed using hNPY 1-36 (American Peptide Co., Sunnyvale, CA) as agonist in order to ascertain functional activity as measured by GTPγ^{35}S binding.

GTPγ^{35}S binding assay: Purified *Sf*9 cell membranes are resuspended by Dounce homogenization (tight pestle) in GTPγ^{35}S binding assay buffer (50 mM Tris pH 7.0, 120 mM NaCl, 2 mM MgCl2, 2 mM EGTA, 0.1% BSA, 0.1 mM bacitracin, 100KIU/mL Aprotinin, 5 μM GDP) and added to reaction tubes at a concentration of 30 μg/reaction tube. After adding

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increasing doses of the agonist hNPY 1-36 (American Peptide Co., Sunnyvale, CA), reactions are initiated by the addition of 100 pM GTPγ^{35}S. Following a 30-minute incubation at ambient temperature, the reactions are terminated by vacuum filtration over GF/C filters (pre-soaked in wash buffer, 0.1% BSA) followed by washing with ice-cold wash buffer (50 mM Tris pH 7.0, 120mM NaCl).

Bound GTPγ^{35}S is determined by liquid scintillation spectrometry of the washed filters. Non-specific binding is determined using 10 mM GTPγS. Data are generally expressed as % maximal response and are derived by determining the maximal agonist stimulated % above basal stimulation. Computer analysis may be conveniently used to calculate estimated EC_{50}, IC_{50} and K_i values from GTPγ^{35}S binding experiment data, e.g., using SigmaPlot software. The binding affinity for the preferred compounds of the invention, expressed as K_i values, ranges from about 0.1 nanomolar to about 5 micromolar. Particularly preferred compounds yield a K_i value of less than 100 nanomolar, most preferably less than 10 nanomolar .

Assay for affinity binding of radiolabeled ligand: Purified membranes are washed with PBS and re-suspended by gentle pipetting in binding buffer (50 mM Tris(HCl), 5 mM KCl, 120 mM NaCl, 2 mM CaCl2, 1 mM MgCl2, 0.1% bovine serum albumin (BSA), pH 7.4). Membranes (5μg) are added to siliconized (Sigmacote, Sigma) polypropylene tubes in addition to 0.050 nM [125I]NPY (porcine, New England Nuclear Corp., Boston, MA) for competition analysis or 0.010-0.500 nM [125I]NPY (porcine) for saturation analysis. For evaluation of guanine nucleotide effects on receptor affinity, GTP is added at a final concentration of 100 μM. Cold displacers are added at concentrations ranging from 10-12 M to 10-6 M to yield a final volume of 0.250 mL. Nonspecific binding is determined in the presence of 1 μM NPY (human, American Peptide Co., Sunnyvale, CA) and accounts for less than 10% of total binding. Following a 2-hour incubation at ambient temperature, the reaction is terminated by rapid vacuum filtration. Samples are filtered over presoaked GF/C Whatman filters (1.0% polyethyleneimine for 2 hours) and rinsed 2 times with 5 mL cold binding buffer lacking BSA. Remaining bound radioactivity is measured by gamma counting. To estimate the Bmax, Kd and Ki, the results of binding experiments are analyzed using SigmaPlot software (SPSS Science, Chicago, IL). The binding affinity for the compounds of the invention, expressed as a Ki value, ranges from about 0.1 nanomolar to about 10

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micromolar. The most preferred compounds of the invention have a Ki of less than 100 nanomolar and a binding selectivity of >100-fold relative to other G-protein coupled receptors, including NPY_5 and CRF_1 receptors.

C. *In vivo* analysis - Food Deprivation

Subjects. Experimentally naive and experienced male Sprague-Dawley rats (Sasco, St. Louis, MO) weighing 210-300g at the beginning of the experiment are used. Animals are triple-housed in stainless steel hanging cages in a temperature (22 C ± 2) and humidity (40-70% RH) controlled animal facility with a 12:12 hour light-dark cycle. Food (Standard Rat Chow, PMI Feeds Inc., #5012) and water are available ad libitum.

Apparatus. Consumption data is collected while the animals are housed in Nalgene Metabolic cages (Model #650-0100). Each cage is comprised of subassemblies made of clear polymethlypentene (PMP), polycarbonate (PC), or stainless steel (SS). All parts disassemble for quick and accurate data collection and for cleaning. The entire cylinder-shaped plastic and SS cage rests on a SS stand and houses one animal.

The animal is contained in the round Upper Chamber (PC) assembly (12cm high and 20cm in diameter) and rests on a SS floor. Two subassemblies are attached to the Upper Chamber. The first assembly consists of a SS feeding chamber (10cm long, 5cm high and 5cm wide) with a PC feeding drawer attached to the bottom. The feeding drawer has two compartments: a food storage compartment with the capacity for approximately 50g of pulverized rat chow, and a food spillage compartment. The animal is allowed access to the pulverized chow by an opening in the SS floor of the feeding chamber. The floor of the feeding chamber does not allow access to the food dropped into the spillage compartment.

The second assembly includes a water bottle support, a PC water bottle (100ml capacity) and a graduated water spillage collection tube. The water bottle support funnels any spilled water into the water spillage collection tube.

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The lower chamber consists of a PMP separating cone, PMP collection funnel, PMP fluid (urine) collection tube, and a PMP solid (feces) collection tube. The separating cone is attached to the top of the collection funnel, which in turn is attached to the bottom of the Upper Chamber. The urine runs off the separating cone onto the walls of the collection funnel and into the urine collection tube. The separating cone also separates the feces and funnels it into the feces collection tube.

Food consumption, water consumption, and body weight may be measured with an Ohaus Portable Advanced scale (±0.1g accuracy).

Procedure. Prior to the day of testing, animals are habituated to the testing apparatus by placing each animal in a Metabolic cage for 1 hour. On the day of the experiment, animals that have been food deprived the previous night are weighed and assigned to treatment groups. Assignments are made using a quasi-random method utilizing the body weights to assure that the treatment groups had similar average body weight. Animals are then administered either vehicle (0.5% methyl cellulose) or drug (a compound of the invention). At that time, the feeding drawer is filled with pulverized chow, the filled water bottle, and the empty urine and feces collection tubes are weighed. Two h after drug treatment, each animal is weighed and placed in a Metabolic Cage. Following a one-hour test session, animals are removed and body weight obtained. The food and water containers are then weighed and the food and water consumption data recorded.

Drugs. Drug suspended in vehicle, or vehicle alone as a control, is administered orally (PO) using a gavage tube connected to a 3 or 5ml syringe at a volume of 10ml/kg. Drug is made into a homogenous suspension by stirring and ultrasonicating for at least 1 hour prior to dosing.

Statistical Analyses. The means and standard errors of the mean (SEM) for food consumption, water consumption, and body weight change are obtained. One-way analysis of variance using Systat (5.2.1) is used to test for group differences. A significant effect is defined as having a p value of $<.05$.

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The following parameters are defined: Body weight change is the difference between the body weight of the animal immediately prior to placement in the metabolic cage and its body weight at the end of the one hour test session. Food consumption is the difference in the weight of the food drawer prior to testing and the weight following the 1-hour test session. Water consumption is the difference in the weight of the water bottle prior to testing and the weight following the 1-hour test session. Preferred compounds of the invention reduce food intake and body weight gain, preferably to a statistically significant degree as determined by standard parametric analysis such as a student's T-test.

Example 262

Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^{3}H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; and Moravek Biochemicals Inc., Brea, CA.

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

Example 263

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Receptor autoradiography

Receptor autoradiography (receptor mapping) is carried out in vitro as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

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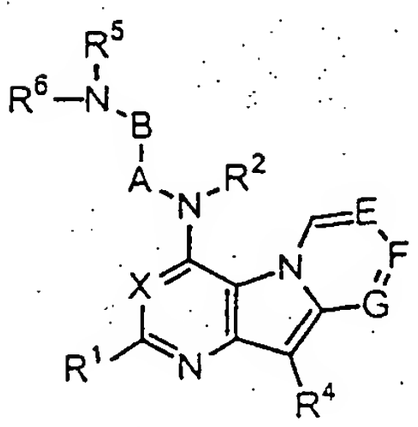
WHAT IS CLAIMED IS:

1. A compound selected from Formula I-XV,



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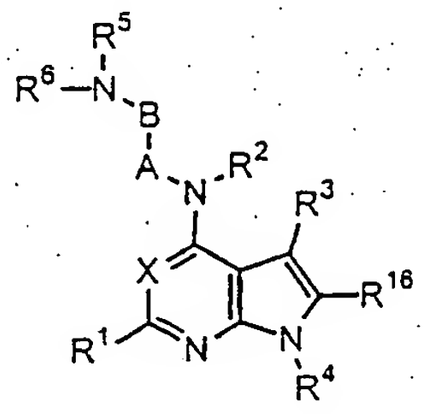

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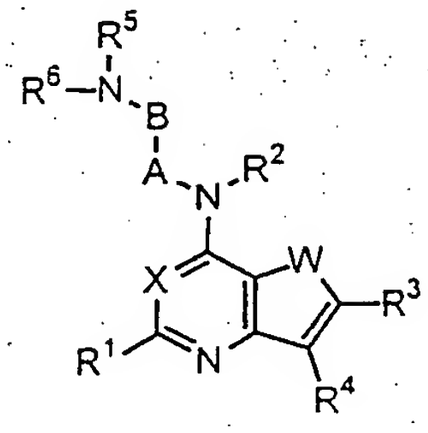

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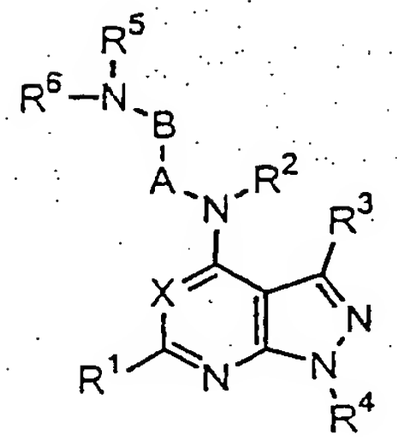

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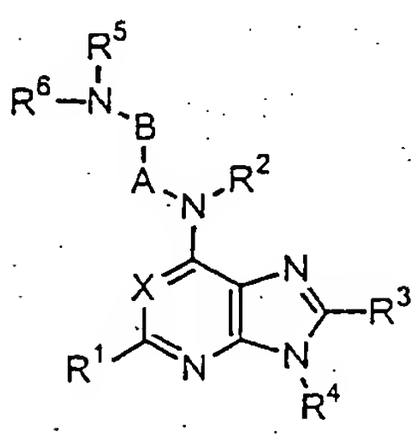

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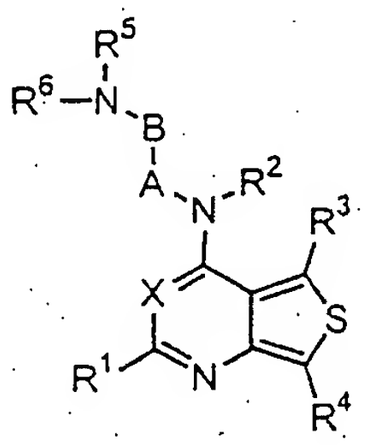

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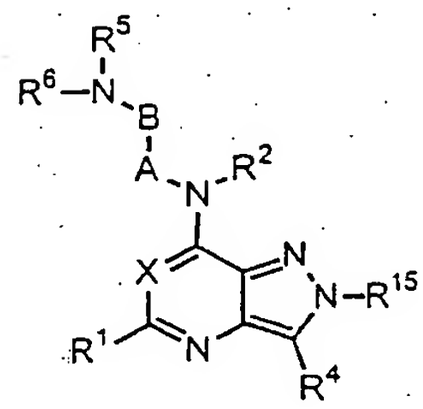

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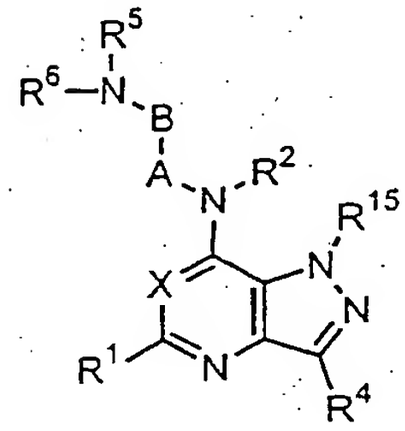

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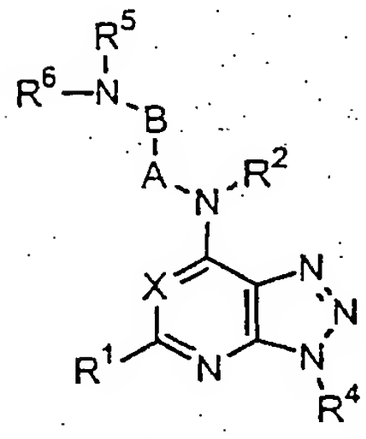

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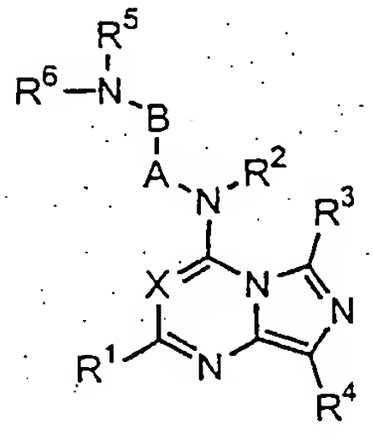

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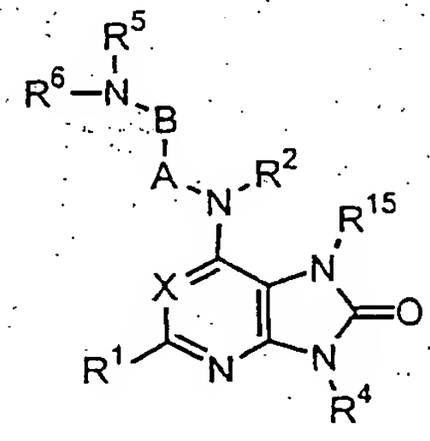

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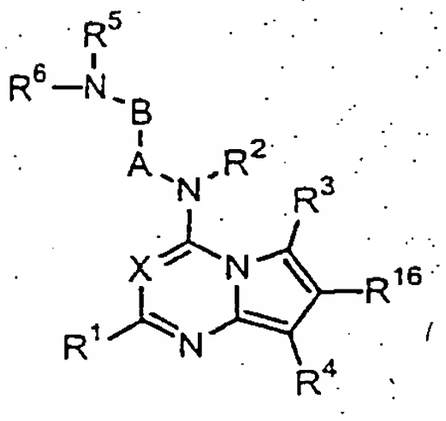
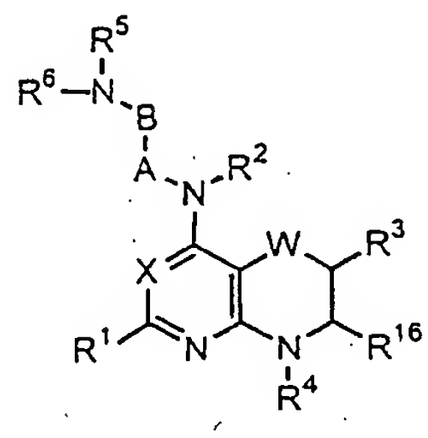


XII



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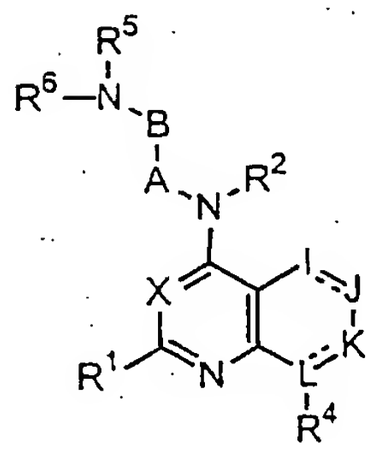
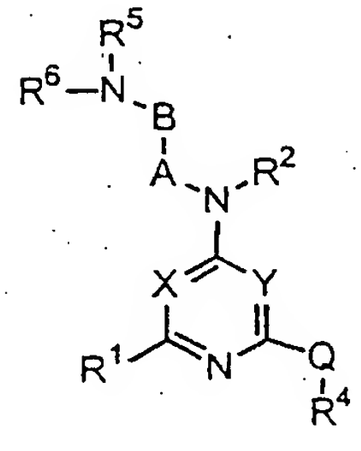


XIV



XV

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or a pharmaceutically acceptable salt thereof, wherein

X is N or CR^{14};

W is S, O, or NR^{15};

Y is N or CR^3;

E, F, and G are each, independently, CR^3 or N;

I and J are each, independently,

C=O, S, O, CR^3R^{16} or NR^{15} when single bonded to both adjacent ring atoms, or

N, or CR^3 when double bonded to an adjacent ring atom;

K is

N or CR^3 when double bonded to L or J, or

O, S, C=O, CR^3R^{16}, or NR^{15} when single bonded to both adjacent ring atoms, or

N or CR^3 when double bonded to an adjacent ring atom;

L is

N or CR^{16} when single bonded to all atoms to which it is attached, or

C (carbon) when double bonded to K;

the 6- or 7-membered ring that contains I, J, K, and L may contain from 1 to 3 double bonds, from 0 to 2 heteroatoms, and from 0 to 2 C=O groups, wherein the carbon atom of such groups are part of the ring and the oxygen atom is a substituent on the ring;

Q is O or NR^{15};

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R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each optionally substituted at each occurrence with R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

or R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted at each position with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted on each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, optionally substituted at each position with R^7

or,

A and R^2 jointly form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle optionally substituted at each position with R^7;

B is $(CH_2)_n$ where n is 1,2 or 3 and is optionally mono- or di-substituted on each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle optionally substituted at each position with R^7;

R^3 and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano,

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halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the heterocyclic core is substituted;

R^5 is selected from:

C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, each of which is substituted with 1 to 5 groups independently selected at each occurrence from halo, C_1-C_2 haloalkyl, OR^7, cyano, NR^8R^9, $CONR^8R^9$, $COOR^7$, $SO_2NR^8R^9$, SO_2R^7, $NR^{11}COR^{12}$, $NR^{11}SO_2R^7$;

C_1-C_6 arylalkyl, C_1-C_6 heteroarylalkyl, C_5-C_8 arylcycloalkyl, or C_5-C_8 heteroarylcycloalkyl, where aryl is phenyl or naphthyl, and heteroaryl is 2-,3-, or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, triazinyl, 1-, 2- or 4-imidazolyl, 2-, 4-, or 5-oxazolyl, isoxazolyl, indolyl, pyrazolyl, quinolyl, isoquinolyl, 2-, 4-, or 5-thiazolyl, benzothiadiazolyl, 1-, 3- or 4-pyrazolyl, 1-, 3- or 4-triazolyl, 2-triazinyl, 2-pyrazinyl, 2-, or 3-furanyl, 2-, or 3-thienyl, 2-, or 3-benzothienyl, or 1-, 2- or 5-tetrazolyl, each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

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C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, each of which is optionally with 1 to 6 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, OR^7, NR^8R^9, with the proviso that when two OR^7 or NR^8R^9 substituents are geminally located on the same carbon R^7 is not H and they can form together a C_2-C_4 ketal, oxazoline, oxazolidine, imidazoline, or imidazolidine heterocycle, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, oxo, hydroximino, C_1-C_6 alkoximino, $SO_2NR^8R^9$, SO_2R^7, heterocycloalkyl, aryl, heteroaryl, where aryl or heteroaryl is optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, NR^8R^9, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that 2 adjacent substituents can optionally form together a C_3-C_{10} cycloalkyl ring, a C_3-C_{10} cycloalkenyl ring or a heterocycloalkyl ring;

or

3- or 4-piperidinyl, 3-pyrrolidinyl, 3- or 4- tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydropyranyl, 3-tetrahydrofuranyl, 3- or 4-tetrahydrothiopyranyl, 3- or 4-(1,1-dioxo) tetrahydrothiopyranyl, 1-azabicyclo[4.4.0]decyl, 8-azabicyclo[3.2.1]octanyl, norbornyl, quinuclidinyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from R^7, C_1-C_6 alkyl-OR^7, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$;

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R^6 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_1-C_6 arylalkyl, C_1-C_6 heteroarylalkyl where aryl or heteroaryl are optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^7$, CN, $SO_2NR^8R^9$, SO_2R^7,

or R^6 and R^2, as mentioned above, jointly form, with the 2 nitrogen atoms to which they are bound, a C_2-C_5 aminoheterocycle optionally substituted at each position with R^7;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,

or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

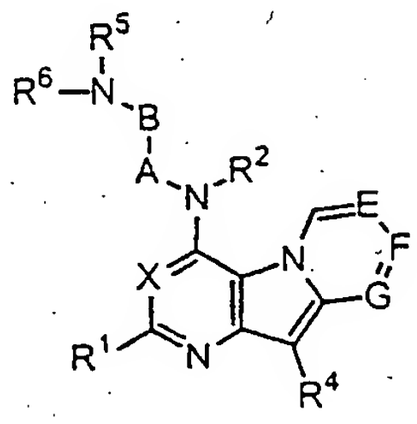
R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that for $SO_2NR^8R^9$, SO_2R^{13}, R^{13} cannot be H;

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN; and

R^{15} is selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 alkyl-OR^7, C_2-C_6 cyanoalkyl, C_2-C_6 alkyl-NR^8R^9.

2. A compound as claimed in claim 1 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

3. A compound as claimed in claim 1 having the formula:



Formula I

wherein A, B, E, F, G, X, R^1, R^2, R^4, R^5, and R^6 are as defined in claim 1.

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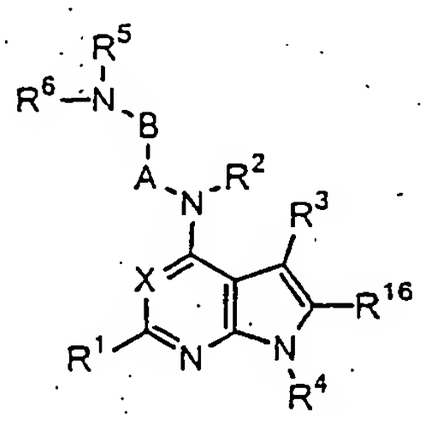
4. A compound as claimed in claim 3 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

5. A compound as claimed in claim 3 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

6 A compound as claimed in claim 1 having the formula:



Formula II

wherein A, B, X, R^1, R^2, R^4, R^5, R^6 and R^{16} are as defined in claim 1.

7. A compound as claimed in claim 6 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

8. A compound as claimed in claim 6 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

9. A compound as claimed in claim 1 having the formula:

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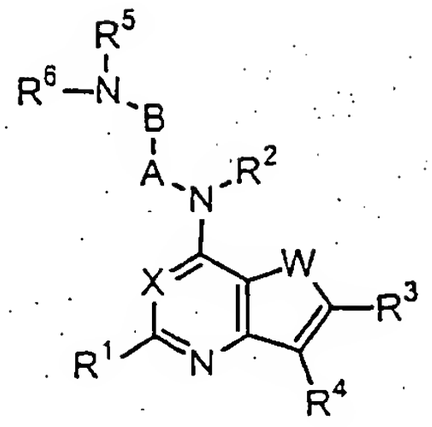


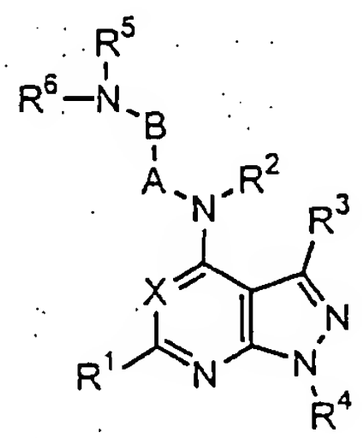
Formula III

wherein A, B, X, W, R^1, R^2, R^4, R^5, and R^6 are as defined in claim 1.

10. A compound as claimed in claim 9 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

11. A compound as claimed in claim 9 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen..

12. A compound as claimed in claim 1 having the formula



Formula IV

wherein A, B, X, R^1, R^2, R^4, R^5, and R^6 are as defined in claim 1.

13. A compound as claimed in claim 12 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl phenethyl optionally substituted with one or two substituents

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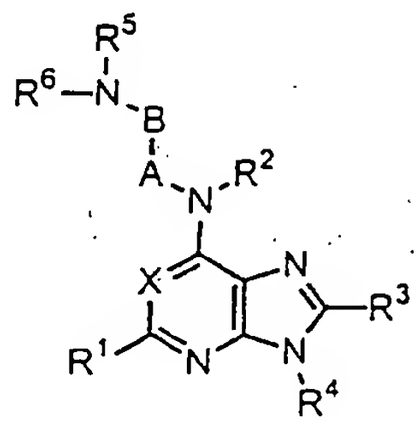
selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

14. A compound as claimed in claim 12 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen..

15. A compound as claimed in claim 1 having the formula



Formula V

wherein A, B, X, R^1, R^2, R^4, R^5, and R^6 are as defined in claim 1.

16. A compound as claimed in claim 15 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl phencthyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

17. A compound as claimed in claim 15 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

.18. A compound as claimed in claim 1 having the formula

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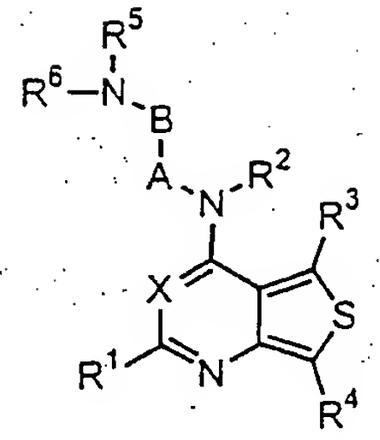


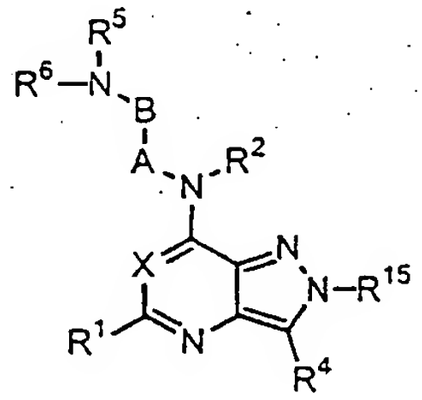
Formula VI

wherein A, B, X, R^1, R^2, R^4, R^5, and R^6 are as defined in claim 1.

19. A compound as claimed in claim 18 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

20. A compound as claimed in claim 18 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

21. A compound as claimed in claim 1 having the formula



Formula VII

wherein A, B, X, R^1, R^2, R^4, R^5, R^6 and R^{15} are as defined in claim 1.

22. A compound as claimed in claim 21 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or

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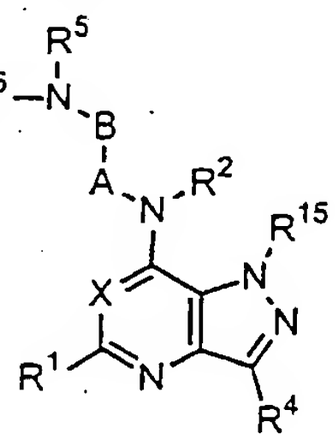
two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

23. A compound as claimed in claim 21 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

.24. A compound as claimed in claim 1 having the formula



Formula VIII

wherein A, B, X, R^1, R^2, R^4, R^5, R^6 and R^{15} are as defined in claim 1.

25 A compound as claimed in claim 24 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

26. A compound as claimed in claim 24 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

.27 A compound as claimed in claim 1 having the formula

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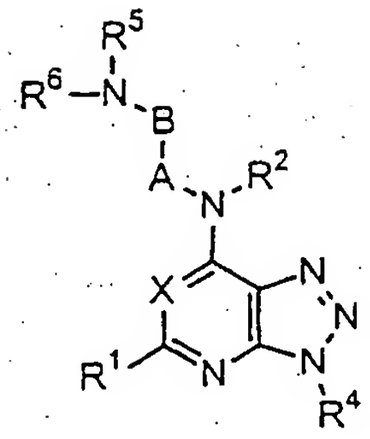


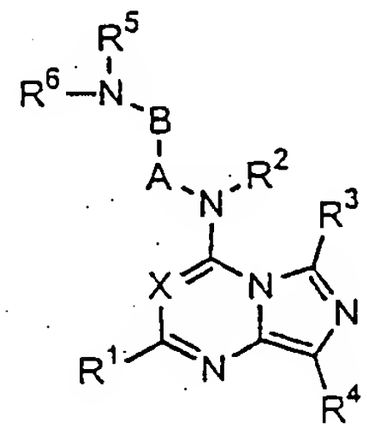
Formula IX

wherein A, B, X, R^1, R^2, R^4, R^5, and R^6 are as defined in claim 1.

28. A compound as claimed in claim 27 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

29. A compound as claimed in claim 27 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

30. A compound as claimed in claim 1 having the formula



Formula X

wherein A, B, X, R^1, R^2, R^4, R^5, and R^6 are as defined in claim 1.

31. A compound as claimed in claim 30 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10}

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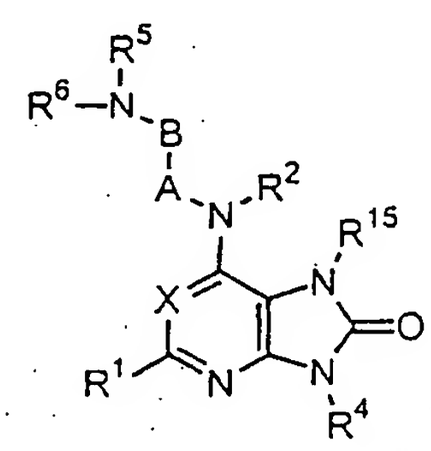
cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

32. A compound as claimed in claim 30 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

33. A compound as claimed in claim 1 having the formula



Formula XI

wherein A, B, X, R^1, R^2, R^4, R^5, R^6 and ^{R15} are as defined in claim 1.

34. A compound as claimed in claim 33 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

35. A compound as claimed in claim 3 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

36. A compound as claimed in claim 1 having the formula

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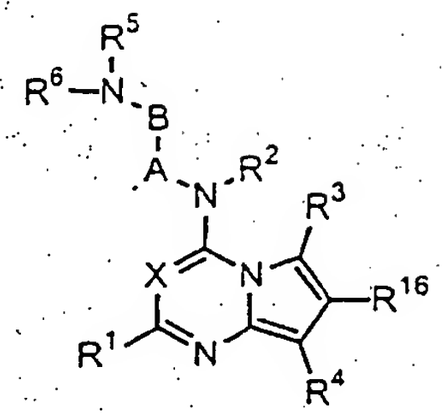


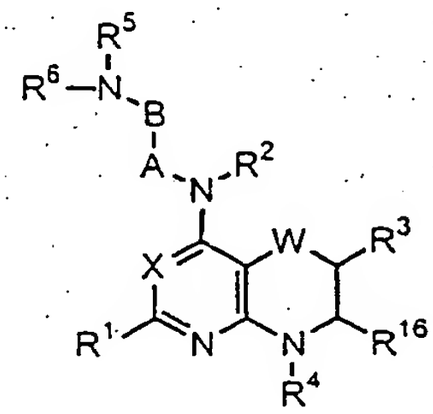
Formula XII

wherein A, B, X, R^1, R^2, R^4, R^5, R^6 and ^{R16} are as defined in claim 1.

37. A compound as claimed in claim 36 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

38. A compound as claimed in claim 36 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

39. A compound as claimed in claim 1 having the formula



Formula XIII

wherein A, B, W, X, R^1, R^2, R^4, R^5, R^6 and ^{R16} are as defined in claim 1.

40. A compound as claimed in claim 39 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or

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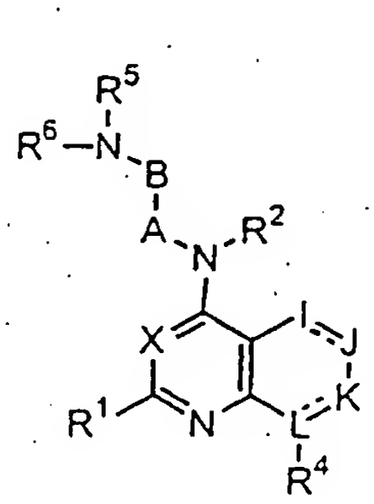
two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

41. A compound as claimed in claim 39 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

42. A compound as claimed in claim 1 having the formula



Formula XIV

wherein A, B, W, X, I, J, K, L, R^1, R^2, R^4, R^5, and R^6 are as defined in claim 1.

43. A compound as claimed in claim 42 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

44. A compound as claimed in claim 42 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

45. A compound as claimed in claim 1 having the formula

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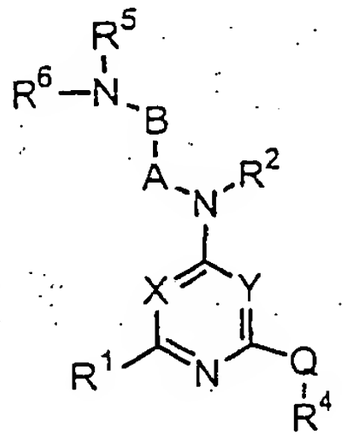

Formula XV

wherein A, B, Q, X, Y, R^1, R^2, R^4, R^5, and R^6 are as defined in claim 1.

46. A compound as claimed in claim 45 wherein X is N or CH, R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, phenethyl optionally substituted with one or two substituents selected from alkyl and alkoxy, tetrahydropyranyl and piperidinyl optionally substituted by a heterocycle.

46. A compound as claimed in claim 45 wherein R^4 is phenyl, optionally substituted in one, two or three positions by alkyl, alkoxy or halogen.

47. A pharmaceutical comprising a compound as claimed in claim 1 for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dislipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disorders, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea..

48. A method of selectively inhibiting binding of NPY_1 receptors, which comprises contacting a compound of claim 1 with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to selectively inhibit binding of NPY_1 receptors in vitro.

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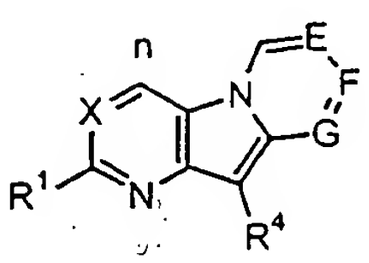
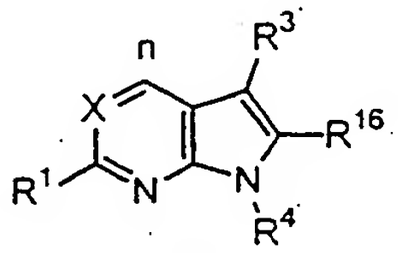
49. A method of treating a physiological disorder or disease selected from the group consisting of disorders or diseases pertaining to the heart, blood vessels or the renal system, such as vasospasm, heart failure, shock, cardiac hypertrophy increased blood pressure, angina, myocardial infarction, sudden cardiac death, arrhythmia, peripheral vascular disease, and abnormal renal conditions such as impaired flow of fluid, abnormal mass transport, or renal failure; conditions related to increased sympathetic nerve activity for example, during or after coronary artery surgery, and operations and surgery in the gastrointestinal tract; cerebral diseases and diseases related to the central nervous system, such as cerebral infarction, neurodegeneration, epilepsy, stroke, and conditions related to stroke, cerebral vasospasm and hemorrhage, depression, anxiety, schizophrenia, and dementia; conditions related to pain or nociception; diseases related to abnormal gastrointestinal motility and secretion, such as different forms of ileus, urinary incontinence, and Crohn's disease; abnormal drink and food intake disorders, such as obesity, anorexia, bulimia, and metabolic disorders; diseases related to sexual dysfunction and reproductive disorders; conditions or disorders associated with inflammation; respiratory diseases, such as asthma and conditions related to asthma and bronchoconstriction; and diseases related to abnormal hormone release, such as leutinizing hormone, growth hormone, insulin, and prolactin, which comprises administering to a person sufferring form such disorder or disease a therapeutically efective amount of a compound as climed in claim 1.

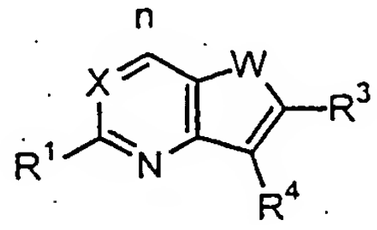
50. A method of converting heterocyclic cores of formula **Ia** to **XVa**



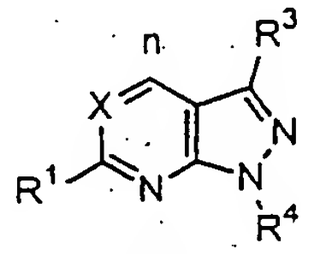
Ia



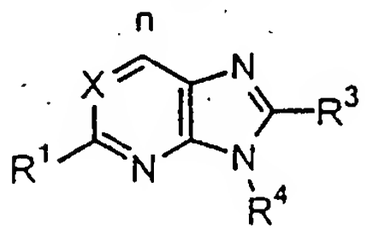
IIa



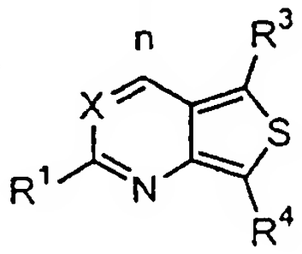
IIIa



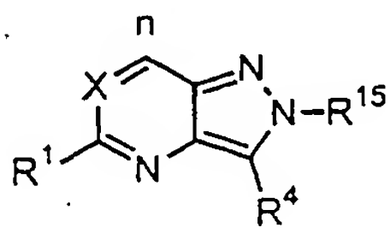
IVa



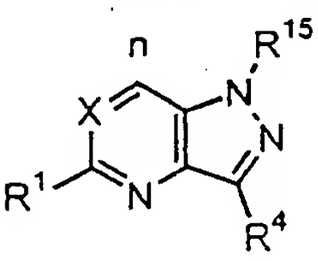
Va



VIa



VIIa



VIIIa

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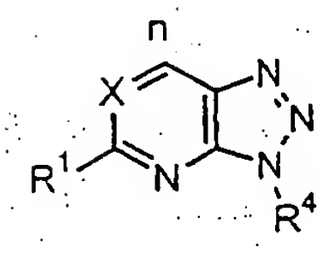
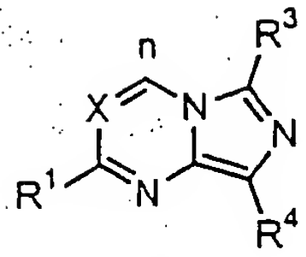
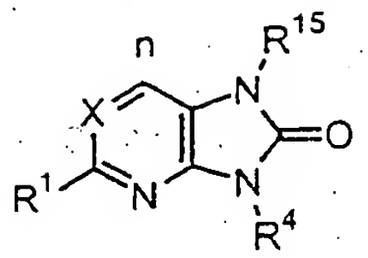


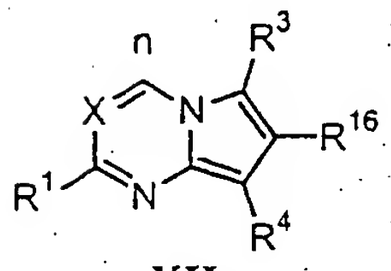
Ixa



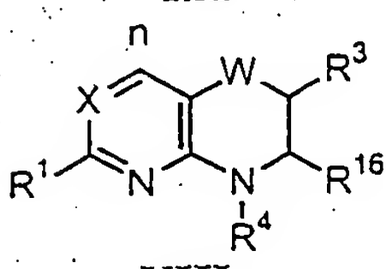
Xa



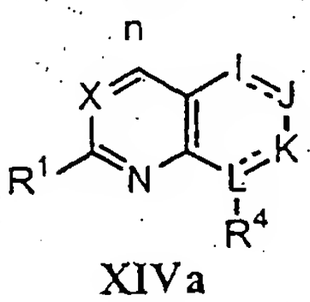
XIa



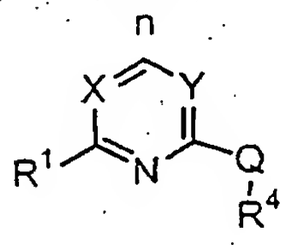
XIIa



XIIIa



XIVa



XVa

where X, E, F, G, W, I, J, K, L, Q, R^1, R^3, R^4, R^{15} and R^{16} are defined per Claim 1, into compounds that potently and selectively interact with NPY_1 receptors by substituting the n-position of heterocycles of formula **Ia - XVIa** with a diamine group of formula $N[R^2]$-A-B-$N[R^6]$-R^5 where R^2, A, B, R^6, and R^5 are defined per Claim 1.

51. A method of treating obesity comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula as defined in claim 1 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug.

52. A method as recited in claim 51 wherein the amount of a compound as defined in claim 1 is about 0.01 mg/kg/day to about 140 mg/kg/day.

53. A method as recited in claim 51 wherein the mammal is female or male human.

54. A pharmaceutical composition which comprises a therapeutically effective amount of compound of claim 1 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

55. A pharmaceutical composition for the treatment of obesity which comprises a therapeutically effective amount of compound of claim 1 or a prodrug thereof or a

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pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

56. A pharmaceutical combination composition comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound of claim 1, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent.

57 A method of treating obesity comprising administering to a mammal in need of such treatment: (a) first compound, said first compound being a compound of claim 1, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; (and (c) wherein the amounts of the first and second compounds result in a therapeutic effect.

58. A kit comprising: (a) first compound, said first compound being a compound of claim 1, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

59. A pharmaceutical combination composition comprising a therapeutically effective amount of a composition comprising (a) first compound, said first compound being a compound of claim 1, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, insulin, metformin, acarbose, a thiazolidinedione, a glitazone, rezulin,

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trogitalazone, a sulfonylurea, glipazide, glyburide, or chlorpropamide; (c) a pharmaceutical carrier, vehicle, or diluent.

60. A pharmaceutical composition comprising a compound as defined in claim 1 for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dislipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disorders, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.

61. A method of selectively inhibiting binding of NPY_1 receptors, which comprises contacting a compound of claim 1 with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to selectively inhibit binding of NPY peptides to NPY_1 receptors in vitro.

62. A compound of claim 1 of formula I and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of :

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,4,6-trimethylphenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-cyclopentyl;

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,6-dichlorophenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-cyclopentyl;

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,4,6-trimethylphenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-(tetrahydropyran-4-yl);

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,6-dichlorophenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-(tetrahydropyran-4-yl);

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a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,4,6-trimethylphenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl);

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,6-dichlorophenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl);

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,4,6-trimethylphenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-$(CH_2)_2$-(3,4-dimethoxyphenyl).

63. A compound of claim 1 of formula II and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me e, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

64. A compound of claim 1 of formula III and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

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a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

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65. A compound of claim 1 of formula IV and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

66. A compound of claim 1 of formula V and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

67. A compound of claim 1 of formula VI and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

68. A compound of claim 1 of formula VII and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

69. A compound of claim 1 of formula VIII and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

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70. A compound of claim 1 of formula IX and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 11-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IX wherein X is CH, R^1 is Me, , R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

71. A compound of claim 1 of formula X and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula X herein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

72. A compound of claim 1 of formula XI and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

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73. A compound of claim 1 of formula XII and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me e, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

74. A compound of claim 1 of formula XIII and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

75. A compound of claim 1 of formula XIV consisting and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group of:

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is N, R^1 is Me-I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is N, R^1 is Me-I=J-K=L- –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

76. A compound of claim 1 of formula XV and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

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a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

77. A method of modulating an NPY receptor by use as a compound of claim 1 of formula I and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of :

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,4,6-trimethylphenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-cyclopentyl;

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,6-dichlorophenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-cyclopentyl;

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a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,4,6-trimethylphenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-(tetrahydropyran-4-yl);

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,6-dichlorophenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-(tetrahydropyran-4-yl);

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,4,6-trimethylphenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl);

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,6-dichlorophenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-(1-(pyrimidin-2-yl)-piperidin-4-yl);

a compound of formula I wherein X is CH or N, R^1 is methyl, R^2 is H, E is CH, F is CH, G is CH, R^4 is 2,4,6-trimethylphenyl, A-B-N[R^6]-R^5 is $(CH_2)_2$-NH-$(CH_2)_2$-(3,4-dimethoxyphenyl).

78. A method of modulating an NPY receptor by use of a compound of claim 1 of formula II and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me e, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula II wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula II wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

79. A method of modulating an NPY receptor by use of a compound of claim 1 of formula III and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene; B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is CH, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is N, W is nitrogen, R^{15} is hydrogen or Me, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is CH, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula III wherein X is N, W is S, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

80. A method of modulating an NPY receptor by use of a compound of claim 1 of formula IV and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula IV wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IV wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

81. A method of modulating an NPY receptor by use of a compound of claim 1 of formula V and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula V wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula V wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

82. A method of modulating an NPY receptor by use of a compound of claim 1 of formula VI and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VI wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VI wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

83. A method of modulating an NPY receptor by use of a compound of claim 1 of formula VII and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

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84. A method of modulating an NPY receptor by use of a compound of claim 1 of formula VIII and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VIII wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula VIII wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

85. A method of modulating an NPY receptor by use of a the compound of claim 1 of formula IX and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 11-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IX wherein X is CH, R^1 is Me, , R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IX wherein X is CH, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula IX wherein X is N, R^1 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

86. A method of modulating an NPY receptor by use of a compound of claim 1 of formula X and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

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a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl

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a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula X wherein X is CH, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula X wherein X is N, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

87. A method of modulating an NPY receptor by use of a compound of claim 1 of formula XI and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula XI wherein X is CH, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XI wherein X is N, R^1 is Me, R^{15} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

88. A method of modulating an NPY receptor by use of a compound of claim 1 of formula XII and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;;

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a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me e, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XII wherein X is CH, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XII wherein X is N, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

89. A method of modulating an NPY receptor by use of a compound of claim 1 of formula XIII and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

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a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIII wherein X is CH, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIII wherein X is N, W is methylene, R^1 is Me, R^3 is H, R^{16} is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

90. A method of modulating an NPY receptor by use of a compound of claim 1 of formula XIV consisting and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group of:

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is N, R^1 is Me-I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-C(Me)=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

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a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

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a compound of formula XIV wherein X is CH, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XIV wherein X is N, R^1 is Me-I=J-K=L- –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XIV wherein X is N, R^1 is Me, -I=J-K=L- is –CH=CH-CH=C-, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

91. A method of modulating an NPY receptor by use of a compound of claim 1 of formula XV and isomers thereof, stereoisomeric forms thereof, or mixture of stereoisomeric forms thereof, and pharmaceutically acceptable salt or prodrug forms thereof, selected from the group consisting of:

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a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

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a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,4,6-trimethylphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XV wherein X is CH, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl;

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a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclopentyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is cyclohexyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is tetrahydropyranyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 3,4-dimethoxyphenethyl;

a compound of formula XV wherein X is N, Y is carbon, Q is oxygen, R^1 is Me, R^3 is Me, R^4 is 2,6-dichloro-4-methoxyphenyl, R^2 is H, A is methylene, B is methylene, R^5 is hydrogen, R^6 is 1-pyrimidin-2-yl-piperidin-4-yl.

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(71) Applicants *(for all designated States except US)*: NEUROGEN CORPORATION [US/US]; 35 Northeast Industrial Road, Branford, CT 06405 (US). PFIZER, INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HORVATH, Raymond, F. [US/US]; 973 Little Meadow, Guilford, CT 06437 (US). TRAN, Jennifer [US/US]; 56 Barier Hill Drive, Guilford, CT 06437 (US). DE LOMBAERT, Stephane [US/US]; 37 Concord Drive, Madison, CT 06443 (US). HODGETTS, Kevin, Julian [US/US]; 224 Reservoir Road, Killingworth, CT 06443 (US). CARPINO, Philip, A. [US/US]; 50 Meridian Street, Groton, CT 06340 (US). GRIFFITH, David, A. [US/US]; 10 Barley Hill Road, Old Saybrook, CT 06475 (US).

(74) Agents: RICHARDS, John; Ladas & Parry, 26 West 61st Sreet, New York, NY 10023 et al. (US).

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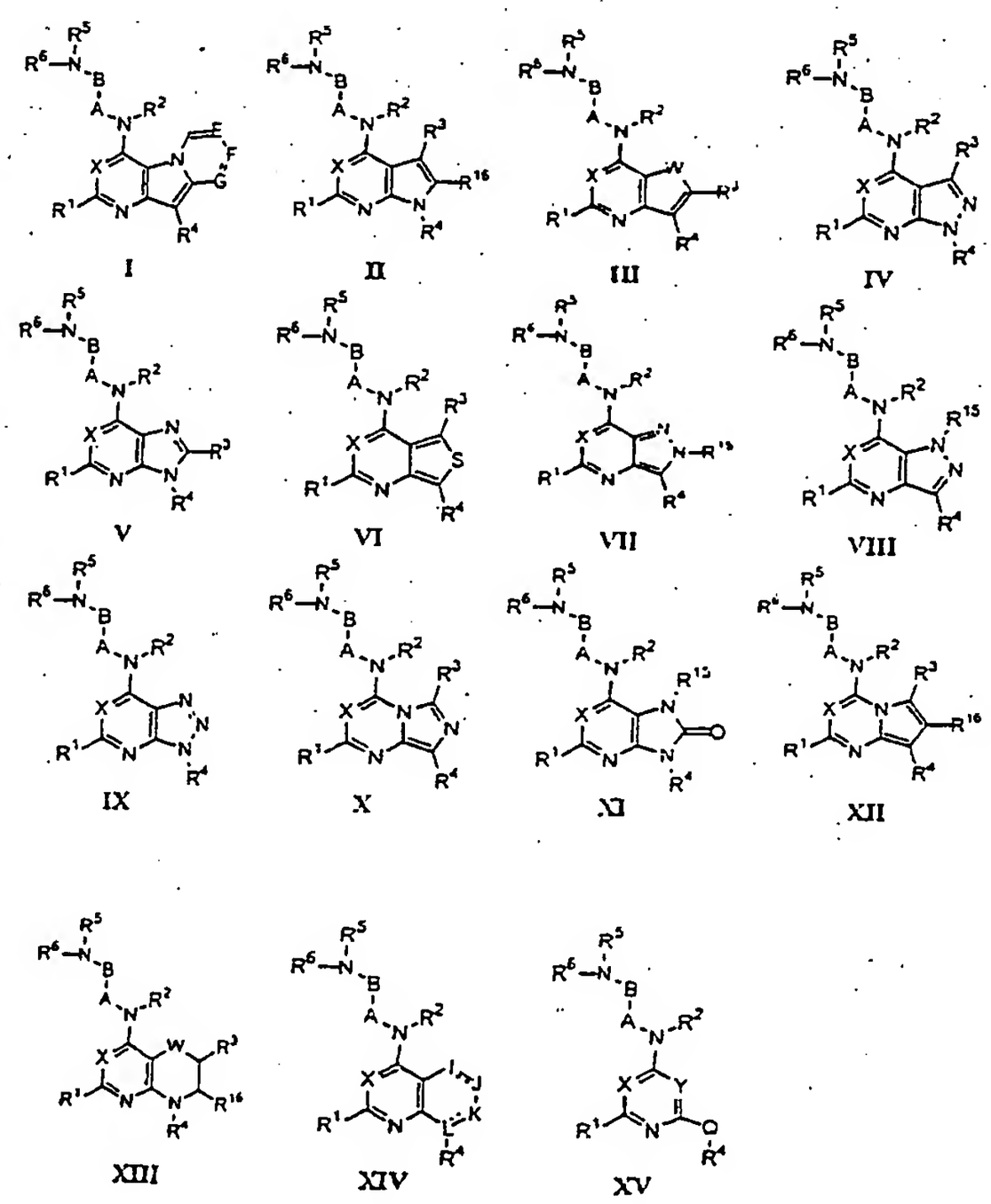
(54) Title: CERTAIN ALKYLENE DIAMINE-SUBSTITUTED HETEROCYCLES



(57) Abstract: The present invention also provides a general method to whereby mono-, bi-, or tri-cyclic heterocycles may be modified to obtain potent antagonists at the NPY_1 receptor. The present invention provides novel, potent, non-peptidic antagonists of NPY receptors, particularly, the NPY_1 receptors, designed from a selection of mono-, bi-, or tri-cyclic heterocyclic cores. This invention relates to novel compounds, compositions, and methods for the treatment of physiological disorders associated with an excess of neuropeptide Y. The novel compounds encompassed by the present invention are those of the formula (I-XV).

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(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

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10 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INSDOCID: <WO___0123389A3_I_>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/26886

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 A61K31/437 A61K31/4365 A61K31/47
A61K31/44 A61P9/00 A61P25/00 C07D471/04 C07D473/34
C07D215/46 C07D213/73 C07D239/48 C07D471/14 C07D495/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 03510 A (DU PONT MERCK PHARMA) 29 January 1998 (1998-01-29) claims 1,66	1,47
A	WO 99 38868 A (DU PONT PHARM CO) 5 August 1999 (1999-08-05) claims 1,7	1,47
A	WO 99 40091 A (AMGEN INC) 12 August 1999 (1999-08-12) claims 1,26	1,47

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2001	22/06/2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/26886

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D475/08 G01N33/566 //(C07D487/04,239:00,209:00), (C07D471/04,235:00,221:00),(C07D487/04,239:00,231:00), (C07D471/04,249:00,221:00),(C07D471/14,221:00,221:00,209:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2001	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/26886

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D471/14,239:00,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2001	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1- 71 (in part)

Present claims 1 to 71 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds where R4 is a phenyl radical substituted as claimed in claim 1 and R5R6N-A-B-N(R2)- represents -NH-CH2-CH2-NH- as illustrated in all examples of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/US 00/26886

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9803510 A	29-01-1998	AU 3894297 A	10-02-1998
		BR 9710544 A	17-08-1999
		CA 2259583 A	29-01-1998
		CN 1225637 A	11-08-1999
		CZ 9900184 A	17-11-1999
		EP 0915880 A	19-05-1999
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		LT 99008 A,B	27-03-2000
		LV 12292 A	20-06-1999
		LV 12292 B	20-11-1999
		NO 990264 A	10-03-1999
		PL 331523 A	19-07-1999
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		AU 2478799 A	16-08-1999
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		EP 1049699 A	08-11-2000
WO 9940091 A	12-08-1999	US 6187777 B	13-02-2001
		AU 2659099 A	23-08-1999
		EP 1054887 A	29-11-2000

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(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basle (CH).

(72) Inventors: BREU, Volker; 9a Leonhard-Mueller-Strasse, 79418 Schliengen (DE). DAUTZENBERG, Frank; 75 Vogesenstrasse, 79379 Muelheim (DE). GUERRY, Philippe; In den Holeematten 2, CH-4102 Binningen (CH). NETTEKOVEN, Matthias, Heinrich; Bandweg 10, 79639 Grenzach-Wyhlen (DE). PFLIEGER, Philippe; 1, rue du Vignoble, F-68130 Schwoben (FR).

(74) Agent: WITTE, Hubert; 124 Grenzacharstrasse, CH-4070 Basle (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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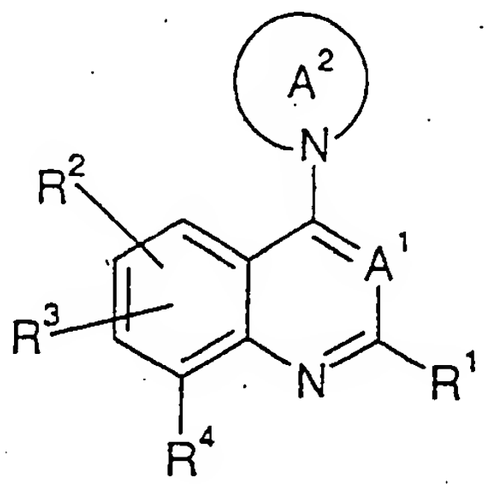
(54) Title: QUINOLINE AND QUINAZOLINE DERIVATIVES

WO 02/20488 A2



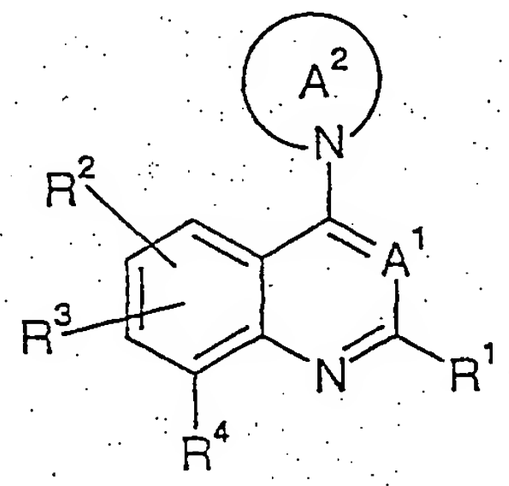
(I)

(57) Abstract: Compounds of formula (I) as well as pharmaceutically usable salts, solvates and esters thereof, wherein R^1, R^2, R^3, R^4, A^1 and A^2 have the significance given in claim 1, can be used in the form of pharmaceutical preparations for the treatment or prevention of arthritis, cardiovascular diseases, diabetes, renal failure, eating disorders and obesity.

Quinoline and quinazoline derivatives

The present invention is concerned with novel quinoline and quinazoline derivatives useful as neuropeptide Y (NPY) receptor ligands, particularly neuropeptide Y (NPY) antagonists.

The invention is concerned especially with compounds of formula I



I

wherein

R^1 is alkyl, cycloalkyl, aralkyl or trifluoroalkyl;

R^2 is hydrogen, alkyl, alkoxy, hydroxy, halogen, trifluoroalkyl, difluoroalkoxy or trifluoroalkoxy;

R^3 is aryl or heteroaryl;

R^4 is hydrogen;

R^5 is hydrogen, alkyl or aralkyl;

R^6 and R^7 are each independently hydrogen or alkyl;

Wb/12.07.01

NSDOCID: <WO___02204BBA2_I_>

A^1 is CH or N;

A^2 is a 4- to 10- membered heterocylic ring optionally substituted with alkyl, hydroxy, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxyalkoxy, -$COOR^5$ or –$CONR^6R^7$;

and pharmaceutically usable salts, solvates and esters thereof.

The compounds of formula I and their pharmaceutically usable salts and are novel and have valuable pharmacological properties. They are neuropeptide ligands, for example neuropeptide receptor antagonists and in particular, they are selective neuropeptides Y Y5 receptor antagonists.

Neuropetide Y is a 36 amino acid peptide that is widely distributed in the central and peripheral nervous systems. This peptide mediates a number of physiological effects through its various receptor subtypes. Studies in animals have shown that neuropeptide Y is a powerful stimulus of food intake, and it has been demonstrated that activation of neuropeptide Y Y5 receptors results in hyperphagia and decreased thermogenesis. Therefore compounds that antagonise neuropetide Y at the Y5 receptor subtype represent an approach to the treatment of eating disorders such as obesity and hyperphagia.

The current approach is aiming at medical intervention to induce weight loss or prevention of weight gain. This is achieved by interfering with appetite control, which is mediated by the Hypothalamus, an important brain region proven to control food intake. Herein, neuropeptide Y (NPY) has been proven to be one of the strongest central mediators of food intake in several animal species. Increased NPY levels result in profound food intake. Various receptors of neuropeptide Y (NPY) have been described to play a role in appetite control and weight gain. Interference with these receptors is likely to reduce appetite and consequently weight gain. Reduction and long-term maintenance of body weight can also have beneficial consequences on con associated risk factors such as arthritis, cardiovascular diseases, diabetes and renal failure.

Accordingly, the compounds of formula I can be used in the prophylaxis or treatment of of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

Objects of the present invention are the compounds of formula I and their aforementioned salts per se and their use as therapeutically active substances, a process for the manufacture of the said compounds, intermediates, pharmaceutical compositions, medicaments containing the said compounds, their pharmaceutically usable salts and

solvates, the use of the said compounds, solvates and salts for the prophylaxis and/or therapy of illnesses, especially in the treatment or prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders such as hyperphagia and particularly obesity, and the use of the said compounds and salts for the production of medicaments for the treatment or prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

In the present description the term "alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1 to 6 carbon atoms and particularly preferred a straight or branched-chain alkyl group with 1 to 4 carbon atoms Examples of straight-chain and branched C_1-C_8 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl and ethyl and most preferred methyl.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C_3-C_8 cycloalkyl are cyclopropyl, methyl-cyclopropyl, dimethylcyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, methyl-cyclohexyl, dimethyl-cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclopropyl and particularly cyclopentyl.

The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec. butoxy and tert.butoxy, 2-hydroxyethoxy, 2-methoxyethoxypreferably methoxy and ethoxy and most preferred methoxy.

The term "alkoxyalkoxy", alone or in combination, signifies a group of the formula alkyl-O-alkyl-O- in which the term "alkyl" has the previously given significance. A preferred example is 2-methoxyethoxy.

The term "hydroxyalkoxy", alone or in combination, signifies alkoxy group as previously described in which one hydrogen atom has been replaced by a hydroxy group. Examples are hydroxymethoxy and preferably 2-hydroxyethoxy.

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group which optionally carries one or more, particularly one to three substituents each independently selected from halogen, trifluoromethyl, amino, alkyl, alkoxy, aryloxy, alkylcarbonyl, cyano, carbamoyl, alkoxycarbamoyl, methylendioxy, carboxy, alkoxycarbonyl, aminocarbonyl,

alkyaminocarbonyl, dialkylaminocarbonyl, hydroxy, nitro and the like, such as phenyl, chlorophenyl, trifluoromethylphenyl, chlorofluorophenyl, aminophenyl, methylcarbonylphenyl, methoxyphenyl, methylendioxyphenyl, 1-naphthyl and 2-naphthyl. Preferred is phenyl. Preferred substituents of phenyl and naphthyl are halogen, trifluoromethyl, amino, alkoxy, methylendioxy, alkylcarbonyl, cyano, alkyl, nitro, hydroxy, trifluoromethoxy, alkylsulfanyl, alkenyl, alkoxycarbonyl, aryloxy, alkoxycarbonylamino, alkylcarbonylamino and aminocarbonyl.

The term "aralkyl", alone or in combination, signifies an alkyl or cycloalkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred are benzyl, benzyl substituted with hydroxy, alkoxy or halogen, preferably fluorine. Particularly preferred is benzyl.

The term "heterocyclyl", alone or in combination, signifies a saturated, partially unsaturated or aromatic 4- to 10-membered heterocycle which contains one or more, preferably one ore two hetero atoms selected from nitrogen, oxygen and sulfur, wherein oxygen and particularly nitrogen are preferred. If desired, it can be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo etc. and/or on a secondary nitrogen atom (i.e. -NH-) by alkyl, cycloalkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e.=N-) by oxido, with halogen, alkyl, cycloalkyl and alkoxy being preferred. Examples of such heterocyclyl groups are pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 3,4-dihydro-1H-isoquinolinyl or azepanyl, wherein each of these rings can be substituted with alkyl. Particularly preferred are pyrrolidinyl, piperidinyl, morpholinyl, 4-methyl-piperazinyl, 3,4-dihydro-1H-isoquinolinyl or azepanyl.

The term "heteroaryl", alone or in combination, signifies aromatic 5- to 10-membered heterocycle which contains one or more, preferably one ore two hetero atoms selected from nitrogen, oxygen and sulfur, wherein nitrogen or oxygen are preferred. If desired, it can be substituted on one or more, preferably on one to three carbon atoms e.g. by halogen, trifluoromethyl, amino, alkoxy, methylendioxy, alkylcarbonyl, cyano, alkyl, nitro, hydroxy, trifluoromethoxy, alkylsulfanyl, alkenyl, alkoxycarbonyl, aryloxy, alkoxycarbonylamino, alkylcarbonylamino or aminocarbonyl. Examples of such heteroaryl groups are thiophenyl, pyridinyl, pyrazinyl and pyrimidinyl, benzofuryl, 1H-indolyl, benzothiophenyl, and benzothiofuranyl. Preferred are thiophenyl, pyridinyl, pyrimidinyl, 1H-indolyl.

The term "amino", alone or in combination, signifies a primary, secondary or tertiary amino group bonded via the nitrogen atom, with the secondary amino group

carrying an alkyl or cycloalkyl substituent and the tertiary amino group carrying two similar or different alkyl or cycloalkyl substituents or the two nitrogen substitutents together forming a ring, such as, for example, $-NH_2$, methylamino, ethylamino, dimethylamino, diethylamino, methyl-ethylamino, pyrrolidin-1-yl or piperidino etc., preferably amino, dimethylamino and diethylamino and particularly primary amino.

The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably fluorine, chlorine or bromine and particularly fluorine or chlorine.

The term "carboxy", alone or in combination, signifies a -COOH group.

The term "cyano", alone or in combination, signifies a -CN group.

The term "nitro", alone or in combination, signifies a $-NO_2$ group.

The term "carboxyalkyl" alone or in combination, signifies an alkyl group as previously described in which one hydrogen atom has been replaced by a carboxy group. The carboxymethyl group is preferred and particularly carboxyethyl.

The term "trifluoroalkyl" alone or in combination, signifies an alkyl group as previously described in which three hydrogen atoms have been replaced by three fluorine atoms. A preferred example is trifluoromethyl.

The term "difluoroalkoxy" alone or in combination, signifies an alkoxy group as previously described in which two hydrogen atoms have been replaced by two fluorine atoms. Examples are $-O-CHF_2$ and $-O-CH_2CHF_2$.

The term "trifluoroalkoxy" alone or in combination, signifies an alkoxy group as previously described in which three hydrogen atoms have been replaced by tree fluorine atoms. Examples are $-O-CF_3$, $-O-CH_2CF_3$. Preferred is $-O-CF_3$.

Examples of pharmaceutically usable salts of the compounds of formula I are salts with physiologically compatible mineral acids such hydrochloric acid, sulfuric acid or phosphoric acid; or with organic acids such as methanesulfonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. Preferred is formic acid. The compounds of formula I with free carboxy groups can also form salts with physiologically compatible bases. Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammonium salts such as the Na, K, Ca or tertramethylammonium salt. The compound of formula I can also be present in the form of zwitterions.

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The compounds of formula I can also be solvated, e.g. hydrated. The solvation can be effected in the course of the manufacturing process or can take place e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of formula I (hydration). The term pharmaceutically usable salts also includes pharmaceutically usable solvates.

The term pharmaceutically usable esters of the compounds of formula I means that compounds of general formula (I) may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compounds in vivo. Examples of such compounds include physiologically acceptable and metabolically labile ester derivatives, such as methoxymethyl esters, methylthiomethyl esters and pivaloyloxymethyl esters. Additionally, any physiologically acceptable equivalents of the compounds of general formula (I), similar to the metabolically labile esters, which are capable of producing the parent compounds of general formula (I) in vivo, are within the scope of this invention.

In more detail, for example, the COOH groups of compounds according to formula I can be esterified. The alkyl and aralkyl esters are examples of suitable esters. The methyl, ethyl, propyl, butyl and benzyl esters are preferred esters. The methyl and ethyl esters are especially preferred. Further examples of pharmaceutically usable esters are compounds of formula I, wherein the hydroxy groups can be esterified. Examples of such esters are formate, acetate, propionate, butyrate, isobutyrate, valerate, 2-methylbutyrate, isovalerate and N,N-dimethylaminoacetate. Preferred esters are acetate and N,N-dimethylaminoacetate.

The term "lipase inhibitor" refers to compounds which are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example orlistat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitor of lipases. Lipstatin is a natural product of microbial origin, and orlistat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compound commonly referred to as panclicins. Panclicins are analogues of orlistat (Mutoh et al, 1994). The term "lipase inhibitor" refers also to polymer bound lipase inhibitors for example described in International Patent Application WO99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterized in that they have been substituted with one or more groups that inhibit lipases. The term "lipase inhibitor" also comprises pharmaceutically acceptable salts of these compounds. The term "lipase inhibitor" preferably refers to orlistat.

Orlistat is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses

processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO 00/09122 and WO 00/09123. Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

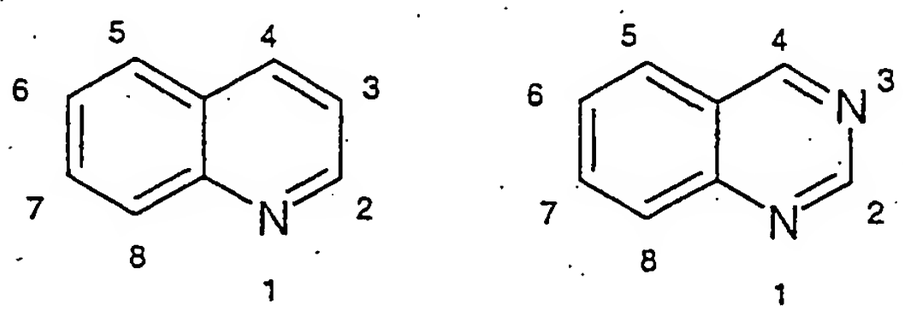
Orlistat is preferably orally administered from 60 to 720 mg per day in divided doses two to three times per day. Preferred is wherein from 180 to 360 mg, most preferably 360 mg per day of a lipase inhibitor is administered to a subject, preferably in divided doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that the lipase inhibitor be administered within about one or two hours of ingestion of a meal containing fat. Generally, for administering a lipase inhibitor as defined above it is preferred that treatment be administered to a human who has a strong family history of obesity and has obtained a body mass index of 25 or greater.

Orlistat can be administered to humans in conventional oral compositions, such as, tablets, coated tablets, hard and soft gelatin capsules, emulsions or suspensions. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatin capsules are lactose, other sugars and sugar alcohols like sorbitol, mannitol, maltodextrin, or other fillers; surfactants like sodium lauryle sulfate, Brij 96, or Tween 80; disintegrants like sodium starch glycolate, maize starch or derivatives thereof; polymers like povidone, crospovidone; talc; stearic acid or its salts and the like. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents and antioxidants. They can also contain still other therapeutically valuable substances. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the pharmaceutical art. Preferably, orlistat is administered according to the formulation shown in the Examples and in U.S. Patent No. 6,004,996, respectively.

The compounds of formula I can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for

example, racemates, optically pure diastereioisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

In the nomenclature used in the present application the ring atoms of the quinoline and the quinazoline rings are numbered as follows:



wherein, R^4 is attached at the 8-position. In a preferred embodiment of the present invention R^3 is attached at the 5- or 6-position. In a particularly preferred embodiment of the present invention R^3 is attached at the 7-position of the quinoline or quinazoline ring.

In another preferred embodiment of the invention R^2 is attached at the 7-position and particularly preferred at the 5- or 6-position.

Preferred are compounds according to formula I and pharmaceutically usable salts and solvates thereof.

Also preferred are compounds of formula I, wherein R^2 is hydrogen, alkyl, alkoxy, hydroxy, trifluoroalkyl, difluoroalkoxy or trifluoroalkoxy. Particularly preferred compounds of formula I are those, wherein R^2 is hydrogen, methyl, methoxy, ethoxy, fluoro, chloro, -O-CHF_2 or –O-CF_3. Most preferred is hydrogen.

Another preferred aspect of the present invention are compounds according to formula I, wherein R^1 is alkyl. Particularly preferred is ethyl and most preferred is methyl.

Likewise preferred are compounds of formula I, wherein A^1 is CH.

Other preferred compounds of formula I are those, wherein A^1 is N.

Further preferred are compounds according to formula I, wherein R^3 is unsubstituted phenyl, thiophenyl, pyridinyl, pyrimidinyl, 1H-indolyl, benzofuryl, benzothiophenyl or naphthyl or R^3 is phenyl, thiophenyl, pyridinyl, pyrimidinyl, 1H-indolyl, benzofuryl, benzothiophenyl or naphthyl, substituted with one to three substituents each independently selected from halogen, trifluoromethyl, amino, alkoxy, methylendioxy, alkylcarbonyl, cyano, alkyl, nitro, hydroxy, trifluoromethoxy,

alkylsulfanyl, alkenyl, alkoxycarbonyl, aryloxy, alkoxycarbonylamino, alkylcarbonylamino and aminocarbonyl.

Further preferred are compounds according to formula I, wherein R^3 is unsubstituted thiophenyl, pyridinyl or naphthyl or R^3 is phenyl or thiophenyl substituted with one or two substituents each independently selected from halogen, trifluoromethyl, alkoxy, alkylcarbonyl, cyano and hydroxy.

Particularly preferred are compounds according to formula I, wherein R^3 is unsubstituted thiophenyl, pyridinyl or naphthyl or R^3 is phenyl or thiophenyl substituted with one or two substituents each independently selected from fluoro, chloro, trifluoromethyl, methoxy, methylcarbonyl, cyano and hydroxy.

Also preferred are compounds according to formula I, wherein R^3 is phenyl or phenyl substituted with one to three substituents, preferably one, each independently selected from halogen, trifluoromethyl, amino, alkoxy, methylendioxy, alkylcarbonyl and cyano or R^3 is thiophenyl, pyridinyl, pyrimidinyl, 1H-indolyl or benzofuryl. Particularly preferred are these compounds, wherein R^3 is phenyl or phenyl substituted with fluoro, chloro, trifluoromethyl, primary amino, methoxy, ethoxy, methylcarbonyl and/or ethylcarbonyl or R^3 is thiophenyl, pyridinyl, pyrimidinyl or 1H-indolyl. Most preferred are these compounds, wherein R^3 is phenyl or phenyl substituted with chloro, trifluoromethyl, primary amino, methoxy, ethoxy and/or methylcarbonyl or R^3 is thiophenyl, pyridinyl, pyrimidinyl or 1H-indolyl.

Also preferred compounds according to formula I are those, wherein A^2 is a 4- to 10-membered heterocylic ring optionally substituted with alkyl. Particularly preferred are those compounds, wherein A^2 is a 5- to 7- membered monocyclic or a 10-membered bicyclic heterocyclic ring optionally substituted with alkyl.

Further preferred are these compounds, wherein A^2 is a pyrrolidine, piperidine, morpholine, piperazine, 3,4-dihydro-1H-isoquinoline or azepane ring, wherein these rings are optionally substituted with alkyl. Most preferred are these compounds, wherein A^2 is a pyrrolidine, piperidine, morpholine, 4-methyl-piperazine, 3,4-dihydro-1H-isoquinoline or azepane ring.

Also preferred are compounds according to formula I, wherein R^5 is hydrogen, methyl, ethyl or benzyl.

Further preferred are compounds of formula I, wherein R^6 and R^7 are hydrogen, methyl or ethyl.

Examples of preferred compounds of formula I are:

7-(3-Chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinoline;

3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenylamine;

1-[4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-ethanone;

2-methyl-7-phenyl-4-pyrrolidin-1-yl-quinoline;

7-(4-methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-thiophen-2-yl-quinoline;

2-methyl-7-pyridin-3-yl-4-pyrrolidin-1-yl-quinoline;

2-methyl-7-pyrimidin-5-yl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-piperidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinoline;

7-(3-chloro-phenyl)-2-methyl-4-piperidin-1-yl-quinoline;

1-[4-(2-methyl-4-piperidin-1-yl-quinolin-7-yl)-phenyl]-ethanone;

3-(2-methyl-4-piperidin-1-yl-quinolin-7-yl)-phenylamine;

7-(4-methoxy-phenyl)-2-methyl-4-piperidin-1-yl-quinoline;

2-methyl-4-piperidin-1-yl-7-thiophen-2-yl-quinoline;

2-methyl-7-phenyl-4-piperidin-1-yl-quinoline;

7-(1H-indol-5-yl)-2-methyl-4-piperidin-1-yl-quinoline;

2-methyl-4-piperidin-1-yl-7-pyridin-3-yl-quinoline;

2-methyl-4-morpholin-4-yl-7-(3-trifluoromethyl-phenyl)-quinoline;

1-[4-(2-methyl-4-morpholin-4-yl-quinolin-7-yl)-phenyl]-ethanone;

2-methyl-4-(4-methyl-piperazin-1-yl)-7-(3-trifluoromethyl-phenyl)-quinoline;

4-(3,4-dihydro-1H-isoquinolin-2-yl)-2-methyl-7-(3-trifluoromethyl-phenyl)-quinoline;

5-(3-chloro-phenyl)-2-methyl-4-piperidin-1-yl-quinoline;

2-methyl-4-piperidin-1-yl-5-(3-trifluoromethyl-phenyl)-quinoline;

5-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

5-(3-chloro-phenyl)-2-methyl-4-morpholin-4-yl-quinoline;

4-azepan-1-yl-2-methyl-7-(3-trifluoromethyl-phenyl)-quinoline;

6-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(3-chloro-phenyl)-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-piperidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinazoline;

7-(4-methoxy-phenyl)-2-methyl-4-piperidin-1-yl-quinazoline;

3-(2-methyl-4-piperidin-1-yl-quinazolin-7-yl)-phenylamine;

2-methyl-4-piperidin-1-yl-7-pyridin-3-yl-quinazoline;

2-methyl-7-pyrimidin-5-yl-4-pyrrolidin-1-yl-quinazoline;

2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinazoline;

7-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinazoline;

7-(3-chloro-phenyl)-2-methyl-4-piperidin-1-yl-quinazoline;

4-azepan-1-yl-2-methyl-7-(3-trifluoromethyl-phenyl)-quinazoline;

7-(4-methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinazoline;

2-methyl-4-pyrrolidin-1-yl-7-thiophen-3-yl-quinazoline;

[4-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenyl]-carbamic acid tert-butyl ester;

3-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-benzonitrile;

7-(3,5-dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinazoline;

1-[3-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenyl]-ethanone;

2-methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethyl-phenyl)-quinazoline;

2-methyl-4-pyrrolidin-1-yl-7-thiophen-2-yl-quinazoline;

1-[5-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-thiophen-2-yl]-ethanone;

7-(1H-indol-5-yl)-2-methyl-4-pyrrolidin-1-yl-quinazoline;

N-[2-methyl-4-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenyl]-acetamide;

2-methyl-7-(3-nitro-phenyl)-4-pyrrolidin-1-yl-quinazoline;

3-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenylamine;

3-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenol;

2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethoxy-phenyl)-quinazoline;

2-methyl-7-phenyl-4-pyrrolidin-1-yl-quinoline;

7-(4-ethyl-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(3,4-dimethoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(2,6-difluoro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(2,4-dimethoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethyl-phenyl)-quinoline;

2-methyl-7-(4-methylsulfanyl-phenyl)-4-pyrrolidin-1-yl-quinoline;

7-(2-methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(3-ethoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

N-[3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-acetamide;

2-methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethoxy-phenyl)-quinoline;

7-benzo[1,3]dioxol-5-yl-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-benzofuran-2-yl-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-benzo[b]thiophen-2-yl-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(3-chloro-4-fluoro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

1-[5-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-thiophen-2-yl]-ethanone;

7-(3,4-dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(2-fluoro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-7-naphthalen-1-yl-4-pyrrolidin-1-yl-quinoline;

7-(2-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-(4-vinyl-phenyl)-quinoline;

7-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-(3-methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-benzoic acid ethyl ester;

4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-benzoic acid ethyl ester;

2-methoxy-4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol;

N-[4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-acetamide;

dimethyl-[4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-amine;

7-(3,5-dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-7-naphthalen-2-yl-4-pyrrolidin-1-yl-quinoline;

N-methyl-4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-benzamide;

3-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol;

2-methoxy-5-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol;

7-(2,6-dimethoxy-pyridin-3-yl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol;

2-methyl-7-(4-phenoxy-phenyl)-4-pyrrolidin-1-yl-quinoline;

7-(2,6-dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethoxy-phenyl)-quinoline and

2-methyl-4-pyrrolidin-1-yl-7-(2-trifluoromethoxy-phenyl)-quinoline.

Examples of particularly preferred compounds of formula I are:

7-(3-Chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinoline;

1-[4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-ethanone;

7-(4-methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-thiophen-2-yl-quinoline;

2-methyl-7-pyridin-3-yl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-piperidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinoline;

5-(3-chloro-phenyl)-2-methyl-4-piperidin-1-yl-quinoline;

4-azepan-1-yl-2-methyl-7-(3-trifluoromethyl-phenyl)-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinazoline;

7-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinazoline;

4-azepan-1-yl-2-methyl-7-(3-trifluoromethyl-phenyl)-quinazoline;

3-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-benzonitrile;

1-[3-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenyl]-ethanone;

7-(3-chloro-4-fluoro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

1-[5-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-thiophen-2-yl]-ethanone;

7-(3,4-dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methoxy-4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol;

7-(3,5-dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline and

2-methyl-7-naphthalen-2-yl-4-pyrrolidin-1-yl-quinoline.

Further preferred compounds of the present invention are:

diethyl-[2-methyl-7-(3-trifluoromethyl-phenyl)-quinolin-4-yl]-amine;

[7-(3-amino-phenyl)-2-methyl-quinolin-4-yl]-diethyl-amine;

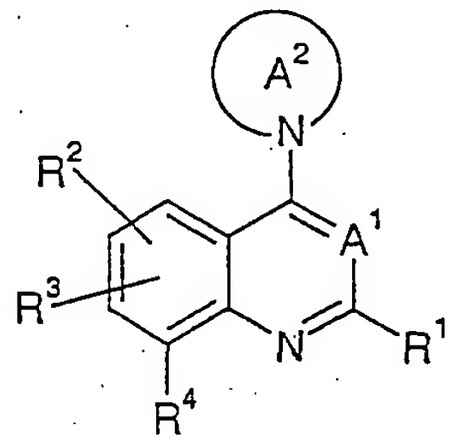
1-[4-(4-diethylamino-2-methyl-quinolin-7-yl)-phenyl]-ethanone;

and pharmaceutically usable salts, solvates and esters thereof.

Processes for the manufacture of compounds of formula I are an object of the invention.

The substituents and indices used in the following description of the processes have the significance given above unless indicated to the contrary.

Compounds of formula I

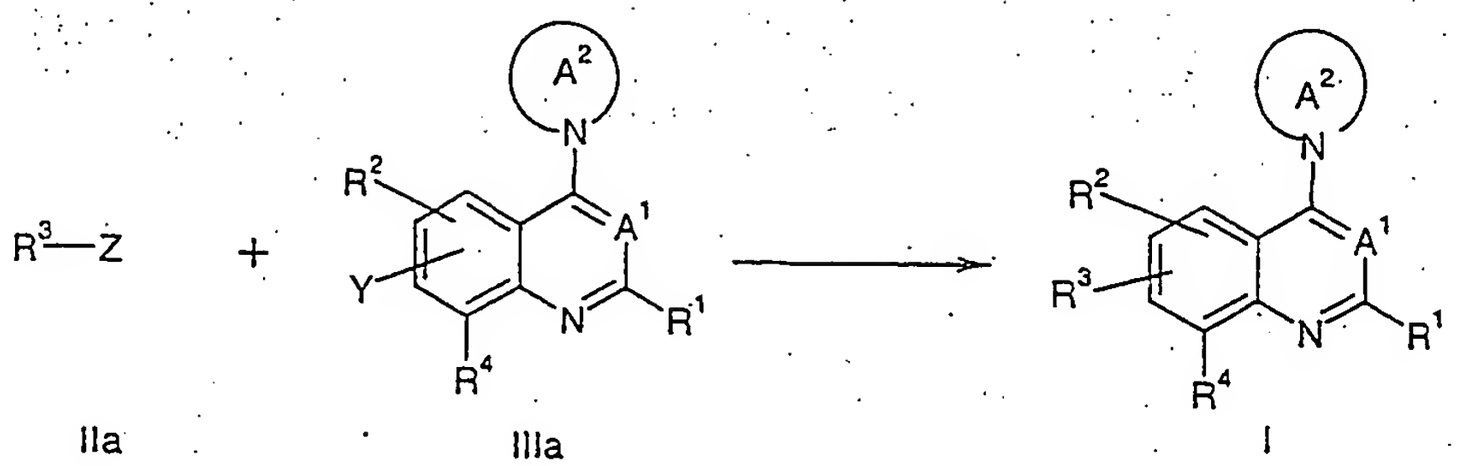


I

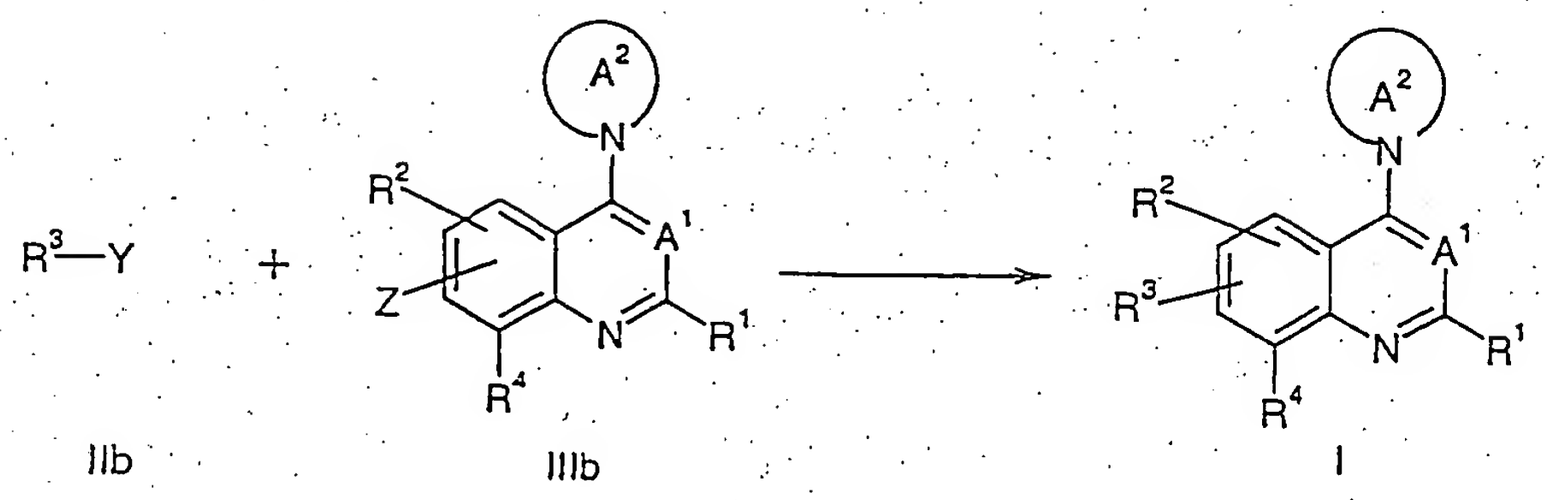
wherein R^1 to R^4, A^1 and A^2 are defined as before can be prepared as follows:

According to scheme A compounds of formula I can be obtained by the reaction of a compound of the general formula IIIa with a compound of formula IIa. Alternatively, compounds of formula I can be prepared as shown in scheme B, wherein a compound of formula IIIb is reacted in the presence of a compound of the formula IIb.

Scheme A



Scheme B



In both schemes, A and B, R^1, R^2, R^3, R^4, A^1 and A^2 are defined as before and Y and Z are substituents or groups which can be used in transition metal catalyzed cross coupling reactions. For example Y can be iodine, bromine, chlorine, methylsulfonyloxy, trifluoromethylsulfonyloxy, phenylsulfonyloxy or p-tosylsulfonyloxy and Z is for example $(OH)_2B$- or $(R'O)_2B$- , wherein R' is methyl, ethyl, isopropyl or the two R' form together a cyclic diester such as 1,3-propyldioxy- or 2,3-dimethyl-2,3-butanedioxy-). (W. Thompson, J. Gaudino, J. Org. Chem. 1984, 49, 5237-5243; T. Ishiyama, M. Murata, N. Miyaura, J. Org. Chem. 1995, 60, 7508-7510). This reaction, also known as a "Suzuki coupling" (N. Miyaura and A. Suzuki, Chem. Rev. 1995, 95, 2457-2483), is preferably effected in an inert organic solvent such as e.g. dimethoxyethane, dioxan, dimethylformamide or tetrahydrofuran at a temperature between about 20°C and the boiling point of the reaction mixture. A further solvent or cosolvent is preferably added to the reaction mixture. Preferably, a base such an alkali metal carbonate, e.g. sodium carbonate, barium

hydroxide, potassium phosphate or potassium fluoride is preferably added as a solid or as an aqueous solution to the reaction mixture. Preferably, the reaction is performed in the presence of a transition metal complex such as a nickel or palladium metal complex, preferably a palladium complex such as tetrakis-triphenylphosphine-palladium or dichloro[1,1'-Bis(diphenylphosphino)-ferrocene]-palladium (II) dichloromethan.

Alternatively, substituent Z in scheme A or B can be

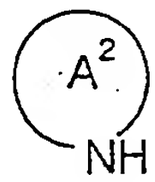
$Sn(alkyl)_3$, e.g. $-Sn(CH_3)_3$ or $-Sn(n\text{-butyl})_3$ ("Stille reaction", J. K. Stille, Angew. Chem. 1986, 98, 504-519; S. P. Stanford, Tetrahedron, 1998, 54, 263-303); or

MgHal or Li("Kharasch" reaction, D. A. Widdowson, Y.-Z. Zhang, Tetrahedron, 1986, 42, 211-2116); or

ZnHal, wherein Hal is bromine, iodine or chlorine; ("Negishi" reaction, E. I. Negishi, Acc. Chem. Res. 1982, 15, 340-348).

The reactions can be effected in the absence of a base in an inert solvent such as e.g. dimethoxyethane, dioxan or tetrahydrofuran at a temperature between about -20°C and the boiling point of the reaction mixture. It can also be advantageous to add an inert salt, especially lithium chloride. A transition metal complex such as a nickel or palladium metal complex, preferably a palladium metal complex can be present in the reaction mixture. A preferred palladium metal complex is tetrakis-triphenylphosphine-palladium.

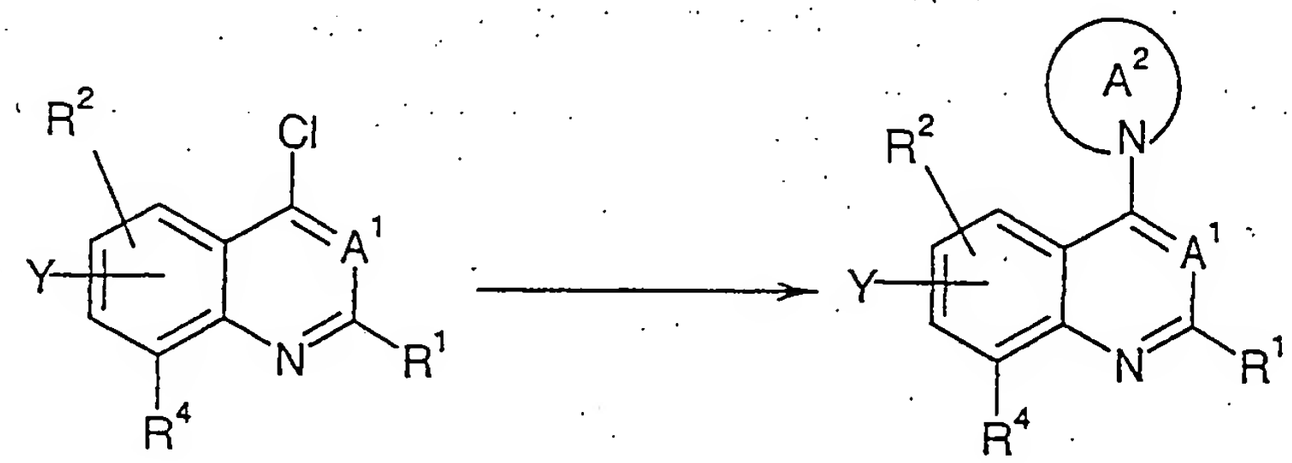
The manufacture of the starting materials of formula III can be effected in a manner known per se, e.g. by reacting a 4-chloroquinoline of type IV or a 4-chloro-quinazoline of type IV with the corresponding amine of formula V



V

conveniently in a polar solvent in the presence of a proton binding reagent at a temperature between 20°C and the boiling point of the reaction mixture. It can be advantageous to add catalytic amounts of an iodide salt, preferably potassium iodide to the reaction mixture. Preferably used solvents are lower alkanol such as methanol or ethanol, isopropanol or n-butanol. Preferably, proton binding reagents are in excess of the amine

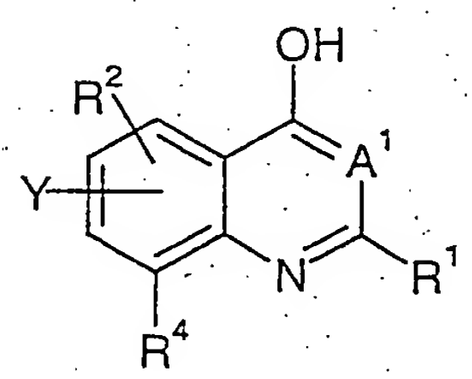
used in the reaction or an organic base such as triethylamin or pyridine or an inorganic base such as alkalimetal carbonates.



IV III

A^1 = CH, N

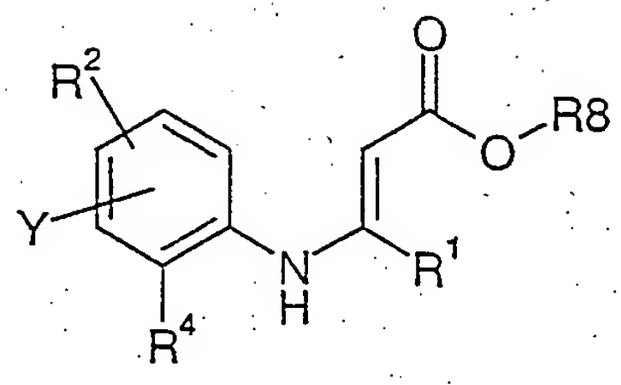
Compounds of formula IV in which R^1, R^2, R^4. A^1 and Y have the above significance and can be prepared by reacting a compound of the general formula



VI

with a halogenating agent, preferably phosphorous oxychloride, which may be used in excess as a solvent for the reaction. An aromatic dialkyl amine can also be used as a cosolvent. The reaction is effected at a temperature between 20°C and the boiling point of the reaction mixture, preferably between 50°C and 110°C. The aromatic dialkyamine is preferably N,N-dimethylaniline.

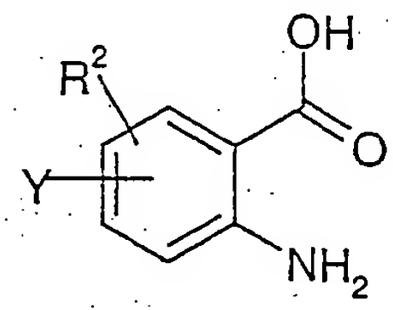
Compounds of formula VI, in which A^1 is CH, and Y, R^1 and R^2 have the above significance can be manufactured by reacting a compound of the general formula



VII

wherein R^1, R^2, R^4 and Y are defined as before and R^8 represents an alkyl group, preferably methyl or ethyl. This cyclisation reaction is preferably effected in an inert organic solvent such as diphenylether or Dowtherm^R A (Eutetic mixture of 26.5% of diphenyl and 73.5% of diphenylether) at a temperature between about 150°C and the boiling point of the reaction mixture in such a way that the alcohol formed during the reaction can be distilled out of the reaction mixture.

Compounds of formula VI, wherein A^1 is N, and Y, R^1, R^2 and R^4 have the above significance can be prepared by reacting a compound of the general formula VIII



VIII

wherein R^2, R^4 and Y are defined as before. This cyclisation reaction is preferably effected in an inert organic solvent such as absolute dimethylformamide by treating an intermediate VIII with an acylchlorid, preferably acetylchlorid (in the case of R^1 is CH_3) e.g. in the presence of an organic base, preferably triethylamine at a temperature between 0°C and 20°C for a short time, e.g. 20 minutes, followed by heating at 90°C for some hours, followed by treatment of the reaction mixture with an ammonium salt, preferably ammonium carbonate at a temperature between 20°C and 100°C. The cyclisation of the anthranilic acid VIII can also be effected by treating VIII in an acid anhydride, preferably acetyl anhydride in the case where R^1 is CH_3, at a temperature between 20°C and boiling temperature of the reaction mixture, followed by treatment of the precipitated intermediate with anhydrous ammonia at temperature between –50°C and –25°C as described in J. Med. Chem. 1993, 36, 733-746.

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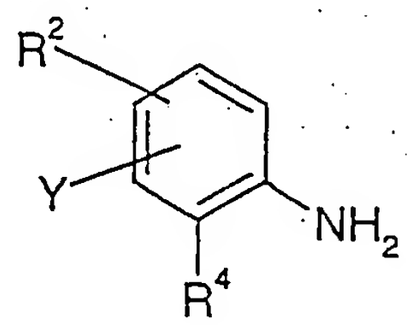
Compounds of formula VII, in which R^1, R^2, R^4, Y and R^8 have the above significance can be prepared by reacting a compound of general formula IX



IX

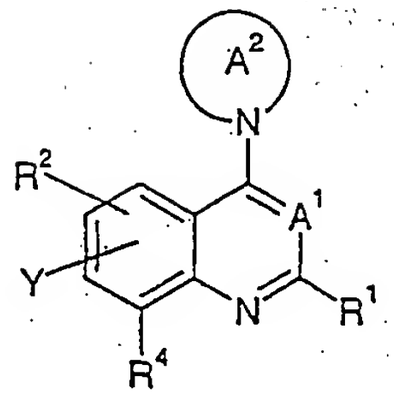
in which R^2, R^4 and Y have the above significance with an appropriate substituted beta-ketoester. The reaction is preferably effected in an inert solvent, e.g. benzene, toluene or cyclohexane at boiling temperature of the reaction mixture. An organic acid, e.g. p-toluensulfonic acid or an inorganic acid, e.g. hydrochlorid acid can be used as a catalyst. The water which is formed during the reaction can be preferably separated from the reaction mixture through azeotropic distillation with e.g. a Dean-Stark water separator. In another variant of the reaction, it is preferably effected in an inert solvent, e.g. benzene, toluene or cyclohexane at room temperature. An organic acid, e.g. p-toluensulfonic acid or an inorganic acid, e.g. hydrochloride acid can be used as a catalyst. The water which is formed during the reaction can be removed from the reaction mixture by treating the reaction mixture with a water-trapping reagent, e.g. molecularsieve.

Compounds of formula VIII, in which R^2 and Y have the above significance can be prepared according to S. E. Webber et al. J. Med. Chem. 1993, 36, 733-746.

The conversion of a compound of formula I into a pharmaceutically usable salt can be carried out by treatment of such a compound with an inorganic acid, for example a hydrohalic acid, such as, for example, hydrochloric acid or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid etc., or with an organic acid, such as, for example, acetic acid, citric acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. The corresponding carboxylate salts can also be prepared from the compounds of formula I by treatment with physiologically compatible bases.

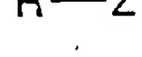
A preferred process for the preparation of a compound of formula I comprises one of the following reactions:

a) the reaction of a compound of formula



IIIa

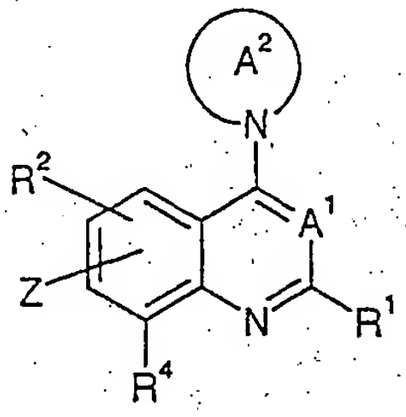
in the presence of a compound of formula



IIa

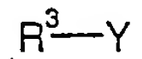
or

b) the reaction of a compound of formula



IIIb

in the presence of a compound of formula



IIb ,

wherein R^1, R^2, R^3, R^4, A^1 and A^2 are defined as before and Y and Z are substituents which can be used in transition metal catalyzed cross coupling reactions. In a preferred aspect the reactions a) and b) are performed in the presence of a transition metal complex such as for example a nickel or palladium metal complex, preferably a palladium metal complex, particularly preferred tetrakis-triphenylphosphine-palladium.

In a further preferred embodiment of the reactions a) and b) Y is iodine, bromine, chlorine, methylsulfonyloxy, trifluoromethylsulfonyloxy, phenylsulfonyloxy or p-tosylsulfonyloxy and Z is $(OH)_2B$- or $(R'O)_2B$- , wherein R' is methyl, ethyl, isopropyl or the two R' form together with the oxygen atoms attached to the boron atom a cyclic diester, preferably 1,3-propyldioxy- or 2,3-dimethyl-2,3-butanedioxy, or Z is -Sn(alkyl)$_3$,

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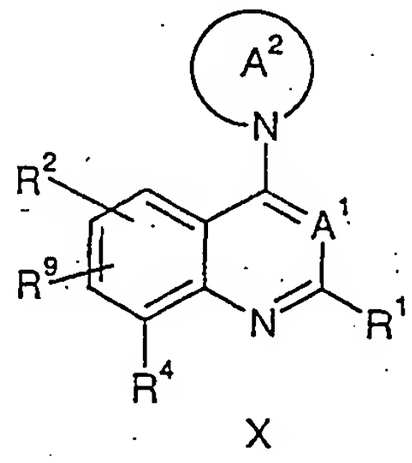
preferably $-Sn(CH_3)_3$ or $-Sn(n\text{-butyl})_3$, or MgHal or Li or ZnHal, wherein Hal is bromine, iodine or chlorine. Particularly preferred are the above reactions a) and b), wherein Y is bromine. Also particularly preferred are the reactions a) and b), wherein Z is $(OH)_2B$- or $-Sn(Me)_3$.

The invention also includes intermediates of formula X



X

wherein R^1, R^2, R^4, A^1 and A^2 are defined as before and, wherein R^9 is iodine, bromine, chlorine, methylsulfonyloxy, trifluoromethylsulfonyloxy, phenylsulfonyloxy or p-tosylsulfonyloxy. Particularly preferred are the compounds of formula X, wherein R^9 is iodine or bromine.

Especially preferred intermediates of formula X are:

7-iodo-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-iodo-2-methyl-4-piperidin-1-yl-quinoline;

diethyl-(7-iodo-2-methyl-quinolin-4-yl)-amine;

7-iodo-2-methyl-4-morpholin-4-yl-quinoline;

7-iodo-2-methyl-4-(4-methyl-piperazin-1-yl)-quinoline;

4-(3,4-dihydro-1H-isoquinolin-2-yl)-7-iodo-2-methyl-quinoline hydrochloride;

5-iodo-2-methyl-4-piperidin-1-yl-quinoline;

5-iodo-2-methyl-4-pyrrolidin-1-yl-quinoline;

5-iodo-2-methyl-4-morpholin-4-yl-quinoline;

4-azepan-1-yl-7-iodo-2-methyl-quinoline;

6-bromo-2-methyl-4-pyrrolidin-1-yl-quinoline;

7-bromo -4-pyrrolidin-1-yl-quinoline;

7-bromo-2-methyl-4-piperidin-1-yl-quinazoline;

7-bromo-2-methyl-4-pyrrolidin-1-yl-quinazoline;

4-azepan-1-yl-7-bromo-2-methyl-quinazoline;

4-azetidin-1-yl-7-bromo-2-methyl-quinazoline;

7-bromo-4-chloro-2-methyl-quinazoline;

4-chloro-5-iodo-2-methyl-quinoline;

6-bromo-4-chloro-2-methyl-quinoline;

7-bromo-2-methyl-3H-quinazolin-4-one;

3-(3-iodo-phenylamino)-but-2-enoic acid ethyl ester.

Further preferred intermediates of the present invention are:

(7-bromo-2-methyl-quinazolin-4-yl)-dimethyl-amine;

(7-bromo-2-methyl-quinazolin-4-yl)-butyl-amine.

The compounds of formula I described above for use as therapeutically active substances are a further object of the invention.

Also an object of the invention are compounds described above for the production of medicaments for the prophylaxis and therapy of illnesses which are caused by disorders associated with the NPY receptor, particularly for the production of medicaments for the prophylaxis and therapy of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

Likewise an object of the invention is a pharmaceutical composition containing a compound of formula I described above and a therapeutically inert carrier. Preferred is this composition comprising further a therapeutically effective amount of a lipase

inhibitor. Particularly preferred is the above composition, wherein the lipase inhibitor is orlistat.

An object of the invention is also the use of the compounds described above for the production of medicaments, particularly for the treatment and prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity.

A further object of the invention comprises compounds which are manufactured according to one of the described processes.

A further object of the invention is a method for the treatment and prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity whereby an effective amount of a compound described above is administered.

According to a further aspect of the invention there is provided a method of treatment of obesity in a human in need of such treatment which comprises administration to the human a therapeutically effective amount of a compound according to formula I and a therapeutically effective amount of a lipase inhibitor, particularly preferred, wherein the lipase inhibitor is orlistat. Also subject of the present invention is the mentioned method, wherein the administration is simultaneous, separate or sequential.

A further preferred embodiment of the present invention is the use of a compound of the formula I in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor, particularly preferred, wherein the lipase inhibitor is orlistat.

Assay Procedures

Cloning of mouse NPY5 receptor cDNAs:

The full-length cDNA encoding the mouse NPY5 (mNPY5) receptor was amplified from mouse brain cDNA using specific primers, designed based on the published sequence, and Pfu DNA-Polymerase (Stratagene). The amplification product was subcloned into the mammalian expression vector pcDNA3 using Eco RI and XhoI

restriction sites. Positive clones were sequenced and one clone, encoding the published sequence was selected for generation of stable cell clones.

Stable transfection:

Human embryonic kidney 293 (HEK293) cells were transfected with 10 µg mNPY5 DNA using the lipofectamine reagent (Gibco BRL) according to the manufacturer's instruction. Two days after transfection, geneticin selection (1 mg/ml) was initiated and several stable clones were isolated. One clone was further used for pharmacological characterization.

Radioligand competition binding:

Human embryonic kidney 293 cells (HEK293), expressing recombinant mouse NPY5-receptor (mNPY5) were broken by three freeze/thawing cycles in hypotonic Tris buffer (5 mM, pH 7.4, 1 mM $MgCl_2$), homogenized and centrifuged at 72,000 x g for 15 min. The pellet was washed twice with 75 mM Tris buffer, pH 7.4, containing 25 mM $MgCl_2$ and 250 mM sucrose, 0.1 mM phenylmethylsulfonylfluoride and 0.1 mM 1,10-pheneanthrolin, resuspended in the same buffer and stored in aliquots at -80°C. Protein was determined according to the method of Lowry using bovine serum albumine (BSA) as a standard.

Radioligand competition binding assays were performed in 250 µl 25 mM Hepes buffer (pH 7.4, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$, 1 % bovine serum albumine, and 0.01 % NaN_3 containing 5 µg protein, 100 pM [^{125}I]labelled peptide YY (PYY) and 10 µL DMSO containing increasing amounts of unlabelled test compounds. After incubation for 1 h at 22°C, bound and free ligand are separated by filtration over glass fibre filters. Non specific binding is assessed in the presence of 1 µM unlabelled PYY. Specific binding is defined as the difference between total binding and non specific binding. IC_{50} values are defined as the concentration of antagonist that displaces 50 % of the binding of [^{125}I]labelled neuropeptide Y. It is determined by linear regression analysis after logit/log transformation of the binding data.

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Results obtained in the foregoing test using representative compounds of the invention as the test compounds are shown in the following table:

Compound	IC_{50}
7-(4-methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline (example 1.6)	0.06 micro Molar
7-(1H-indol-5-yl)-2-methyl-4-piperidin-1-yl-quinoline (example 1.17)	0.10 micro Molar

Preferred compounds as described above have IC_{50} values below 1000 nM; more preferred compounds have IC_{50} values below 100 nM, particularly below 10 nM. Most preferred compounds have IC_{50} values below 1 nM. These results have been obtained by using the foregoing test.

The compounds of formula I and their pharmaceutically usable salts, solvates and esters can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula I and their pharmaceutically usable salts, solvates and esters can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées and hard gelatin capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées and hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

In accordance with the invention the compounds of formula I and their pharmaceutically usable salts, solvates and esters can be used for the prophylaxis and treatment of arthritis, cardiovascular diseases, diabetes, renal failure and particularly eating disorders and obesity. The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 20 mg per kg body weight, preferably about 0.5 mg to 4 mg per kg body weight (e.g. about 300 mg per person), divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts, should be appropriate. It will, however, be clear that the upper limit given above can be exceeded when this is shown to be indicated.

The invention is illustrated hereinafter by Examples, which have no limiting character.

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Examples

Example 1.1:

Preparation of 7-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline:

A mixture of 1.5 g 7-iodo-2-methyl-4-pyrrolidin-1-yl-quinoline (Example 3.1),256 mg tetrakis(triphenylphosphine) palladium and 30 ml Dimethoxyethane is stirred under argon for 15 min. 1.04 g 3-Chlorophenylboronic acid and 7 ml Ethanol are added. The resulting red solution is stirred for another 10 min. at room temperature and treated afterwards with 19 ml of a 2M aqueous solution of sodium carbonate. The mixture is refluxed for 1.5 h under vigorous stirring. After the reaction is complete, the reaction mixture is concentrated on a rotary evaporator. The residue is taken up in 50 ml water and extracted twice with 50 ml ethyl acetate. The combined organic phases are washed with 50 ml saturated aqueous solution of sodium chloride, dried over magnesium sulfate and filtered. The filtrate is evaporated and the residue is chromatographed on silica gel (eluent: Dichloromethane/Methanol 19:1 then 4:1). The pure fractions are combined and evaporated. 1.235g of 7-(3-Chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline are obtained as a colorless oil. MS (ISP): 323.3 $(M+H)^+$.

The following compounds were prepared in analogy to Example 1.1.:

Example 1.2:

In analogy with Example 1.1) with 3-trifluoromethylphenylboronic acid there is obtained 2-Methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinoline as a yellowish foam. MS (ISP): 357.3 $(M+H)^+$.

Example 1.3 :

In analogy with Example 1.1) with 3-aminophenylboronic acid there is obtained 3-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenylamine as a beige foam. MS (EI): peaks at m/e: 303 (M+, 100%), 274 (14%), 260 (9%).

Example 1.4:

In analogy with Example 1.1) with 4-acetylphenylboronic acid there is obtained 1-[4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-ethanone as a slightly brown foam. MS (ISP): 331.3 $(M+H)^+$.

Example 1.5 :

In analogy with Example 1.1) with phenylboronic acid there is obtained 2-methyl-7-phenyl-4-pyrrolidin-1-yl-quinoline as a yellowish foam. MS (ISP): 289.3 $(M+H)^+$.

Example1.6 :

In analogy with Example 1.1) with 4-methoxyphenylboronic acid there is obtained 7-(4-methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline as a white foam. MS (ISP): 319.4 $(M+H)^+$.

Example 1.7 :

In analogy with Example 1.1) with 2-thiopheneboronic acid there is obtained 2-methyl-4-pyrrolidin-1-yl-7-thiophen-2-yl-quinoline as a beige foam. MS (ISP): 295.3 $(M+H)^+$.

Example 1.8 :

In analogy with Example 1.1) with pyridine-3-boronic acid 1,3-propane-diol cyclic ester there is obtained 2-Methyl-7-pyridin-3-yl-4-pyrrolidin-1-yl-quinoline as a yellowish foam. MS (ISP): 290.3 $(M+H)^+$.

Example 1.9:

In analogy with Example 1.1) with 5-pyrimidinylboronic acid (Chem. Scr. 1986, 26, 305-309) there is obtained 2-methyl-7-pyrimidin-5-yl-4-pyrrolidin-1-yl-quinoline as a light yellow solid. MS (ISP): 290.3 $(M+H)^+$.

Example 1.10:

In analogy with Example 1.1) with 3-trifluoromethylphenylboronic acid and 7-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.2) there is obtained 2-methyl-4-piperidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinoline as a yellow foam. MS (ISP): 371.3 $(M+H)^+$.

Example 1.11:

In analogy with Example 1.1) with 3-chlorophenylboronic acid and 7-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.2) there is obtained 7-(3-chloro-phenyl)-2-methyl-4-piperidin-1-yl-quinoline as a yellow foam. MS (EI): peaks at m/e: 337 (M+, 45%), 335(100%), 279 (9%).

Example 1.12:

In analogy with Example 1.1) with 4-acetylphenylboronic acid and and 7-Iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.2) there is obtained 1-[4-(2-methyl-4-piperidin-1-yl-quinolin-7-yl)-phenyl]-ethanone as a yellow foam. MS (ISP): 345.4 $(M+H)^+$.

Example 1.13:

In analogy with Example 1.1) with 3-aminophenylboronic acid and 7-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.2) there is obtained 3-(2-methyl-4-piperidin-1-yl-quinolin-7-yl)-phenylamine as a slightly brown solid. MS (EI): peaks at m/e: 317 (M+, 100%), 260 (8%), 234 (9%).

Example 1.14:

In analogy with Example 1.1) with 4-methoxyphenylboronic acid and 7-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.2) there is obtained 7-(4-methoxy-phenyl)-2-methyl-4-piperidin-1-yl-quinoline as a slightly orange foam. MS (ISP): 333.3$(M+H)^+$.

Example 1.15:

In analogy with Example 1.1) with 2-thiophenboronic acid and 7-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.2) there is obtained 2-methyl-4-piperidin-1-yl-7-thiophen-2-yl-quinoline as a yellow solid. Mp. 122-123°C. MS (ISP): 309.2$(M+H)^+$.

Example 1.16:

In analogy with Example 1.1) with phenylboronic acid and 7-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.2) there is obtained 2-methyl-7-phenyl-4-piperidin-1-yl-quinoline as a yellow solid. Mp. 111-112°C. MS (EI): peaks at m/e: 302 (M+, 100%), 245 (12%), 219(10%).

Example 1.17:

In analogy with Example 1.1) with 1H-indol-5-ylboronic acid (Heterocycles, 1992, 34, 1169-1175) and 7-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.2) there is obtained 7-(1H-Indol-5-yl)-2-methyl-4-piperidin-1-yl-quinoline as a slightly brown solid. MS (ISP): 342.3$(M+H)^+$.

Example 1.18 :

In analogy with Example 1.1) with pyridine-3-boronic acid 1,3-propanediol cyclic ester and 7-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.2) there is obtained 2-methyl-4-piperidin-1-yl-7-pyridin-3-yl-quinoline as a yellow foam. MS (ISP): 304.3$(M+H)^+$.

Example 1.19:

In analogy with Example 1.1) with 3-trifluoromethylphenylboronic acid and diethyl-(7-iodo-2-methyl-quinolin-4-yl)-amine (Example 3.3) there is obtained diethyl-[2-methyl-7-(3-trifluoromethyl-phenyl)-quinolin-4-yl]-amine as a colorless oil. MS (ISP): 359.2$(M+H)^+$.

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Example 1.20:

In analogy with Example 1.1) with 3-aminophenylboronic acid and diethyl-(7-iodo-2-methyl-quinolin-4-yl)-amine (Example 3.3) there is obtained [7-(3-amino-phenyl)-2-methyl-quinolin-4-yl]-diethyl-amine as a slightly orange oil. MS (ISP): 306.3$(M+H)^+$.

Example 1.21:

In analogy with Example 1.1) with 4-acetylphenylboronic acid and diethyl-(7-iodo-2-methyl-quinolin-4-yl)-amine (Example 3.3) there is obtained 1-[4-(4-diethylamino-2-methyl-quinolin-7-yl)-phenyl]-ethanone as a slightly orange oil. MS (ISP): 333.3$(M+H)^+$.

Example 1.22:

In analogy with Example 1.1) with 3-trifluoromethylphenylboronic acid and 7-Iodo-2-methyl-4-morpholin-4-yl-quinoline (Example 3.4) there is obtained 2-methyl-4-morpholin-4-yl-7-(3-trifluoromethyl-phenyl)-quinoline as a yellow foam. MS (EI): peaks at m/e: 372 (M+, 100%), 314 (67%), 169(19%).

Example 1.23:

In analogy with Example 1.1) with 4-acetylphenylboronic acid and 7-iodo-2-methyl-4-morpholin-4-yl-quinoline (Example 3.4) there is obtained 1-[4-(2-methyl-4-morpholin-4-yl-quinolin-7-yl)-phenyl]-ethanone as a slightly red foam. MS (ISP): 347.3$(M+H)^+$.

Example 1.24:

In analogy with Example 1.1) with 3-trifluoromethylphenylboronic acid and 7-iodo-2-methyl-4-(4-methyl-piperazin-1-yl)-quinoline (Example 3.5) there is obtained 2-methyl-4-(4-methyl-piperazin-1-yl)-7-(3-trifluoromethyl-phenyl)-quinoline as an orange foam. MS (EI): peaks at m/e: 385(M+, 57%), 370 (19%), 42(100%).

Example 1.25:

In analogy with Example 1.1) with 3-trifluoromethylphenylboronic acid and 4-(3,4-dihydro-1H-isoquinolin-2-yl)-7-iodo-2-methyl-quinoline hydrochloride (Example 3.6) there is obtained 4-(3,4-dihydro-1H-isoquinolin-2-yl)-2-methyl-7-(3-trifluoromethyl-phenyl)-quinoline as a light-yellow foam. MS (ISP): 419.3$(M+H)^+$.

Example 1.26:

In analogy with Example 1.1) with 3-chlorophenylboronic acid and 5-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.7) there is obtained 5-(3-chloro-phenyl)-2-methyl-4-piperidin-1-yl-quinoline as a colourless viscous oil. MS (EI): peaks at m/e: 336(M+, 100%), 307 (17%), 277(32%), 225 (49%).

Example 1.27:

In analogy with Example 1.1) with 3-trifluoromethylphenylboronic acid and 5-iodo-2-methyl-4-piperidin-1-yl-quinoline (Example 3.7) there is obtained 2-methyl-4-piperidin-1-yl-5-(3-trifluoromethyl-phenyl)-quinoline as a yellow foam. MS (ISP): 371.4$(M+H)^+$.

Example 1.28:

In analogy with Example 1.1) with 3-chlorophenylboronic acid and 5-iodo-2-methyl-4-pyrrolidin-1-yl-quinoline (Example 3.8) there is obtained 5-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline as a light-yellow amorphous solid. MS (ISP): 323.3$(M+H)^+$.

Example 1.29:

In analogy with Example 1.1) with 3-chlorophenylboronic acid and 5-Iodo-2-methyl-4-morpholin-1-yl-quinoline (Example 3.9) there is obtained 5-(3-chloro-phenyl)-2-methyl-4-morpholin-4-yl-quinoline as a colorless viscous oil. MS (EI): peaks at m/e: 338(M+, 87%), 277(100%), 245 (37%).

Example 1.30:

In analogy with Example 1.1) with 3-trifluoromethylphenylboronic acid and 4-azepan-1-yl-7-iodo-2-methyl-quinoline (Example 3.10) there is obtained 4-azepan-1-yl-2-methyl-7-(3-trifluoromethyl-phenyl)-quinoline as a yellowish foam. MS (ISP): 385.3 $(M+H)^+$.

Example 1.31:

In analogy with Example 1.1) with 3-chlorophenylboronic acid and 6-bromo-2-methyl-4-pyrrolidin-1-yl-quinoline (Example 3.11) there is obtained 6-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline as a yellowish gum. MS (ISP): 323.3 $(M+H)^+$.

Example 1.32:

In analogy with Example 1.1) with 3-chlorophenylboronic acid and 7-bromo-4-pyrrolidin-1-yl-quinoline (Example 3.12) there is obtained 7-(3-chloro-phenyl)-4-pyrrolidin-1-yl-quinoline as a beige amorphous solid. MS (ISP): 309.2 $(M+H)^+$.

Example 2.1:

Preparation of 2-Methyl-4-piperidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinazoline:

In analogy with Example 1.1) with 3-trifluoromethylphenylboronic acid and 7-bromo-2-methyl-4-piperidin-1-yl-quinazoline (Example 4.1) there is obtained 2-methyl-4-piperidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinazoline as a light-yellow solid. MS (EI): peaks at m/e: 371(M+, 76%), 342 (100%), 288(57%).

Example 2.2:

In analogy with Example 1.1) with 4-methoxyphenylboronic acid and 7-bromo-2-methyl-4-piperidin-1-yl-quinazoline (Example 4.1) there is obtained 7-(4-methoxy-phenyl)-2-methyl-4-piperidin-1-yl-quinazoline as a light-yellow oil. MS (ISP): 434.3$(M+H)^+$.

Example 2.3:

In analogy with Example 1.1) with 3-aminophenylboronic acid and 7-bromo-2-methyl-4-piperidin-1-yl-quinazoline (Example 4.1) there is obtained 3-(2-methyl-4-piperidin-1-yl-quinazolin-7-yl)-phenylamine as a light-yellow solid. MS (ISP): 319.4$(M+H)^+$.

Example 2.4:

In analogy with Example 1.1) with pyridine-3-boronic acid 1,3-propanediol cyclic ester and 7-bromo-2-methyl-4-piperidin-1-yl-quinazoline (Example 4.1) there3 is obtained 2-methyl-4-piperidin-1-yl-7-pyridin-3-yl-quinazoline as a light-yellow solid. MS (ISP): 305.3$(M+H)^+$.

Example 2.5:

In analogy with Example 1.1) with 5-Pyrimidinylboronic acid (Chem. Scr. 1986, 26, 305-309) and 7-bromo-2-methyl-4-pyrrolidin-1-yl-quinazoline (Example 4.2) there is obtained 2-methyl-7-pyrimidin-5-yl-4-pyrrolidin-1-yl-quinazoline as a light-yellow solid. MS (ISP): 292.3$(M+H)^+$.

Example 2.6:

In analogy with example 1.1) with 3-trifluoromethylphenylboronic acid and 7-bromo-2-methyl-4-pyrrolidin-1-yl-quinazoline (Example 4.2) there is obtained 2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinazoline as a light-yellow foam. MS (ISP): 358.2$(M+H)^+$.

Example 2.7:

In analogy with example 1.1) with 3-chlorophenyl boronic acid and 7-bromo-2-methyl-4-pyrrolidin-1-yl-quinazoline (Example 4.2) there is obtained 7-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinazoline as a white solid. MS (ISP): 324.3$(M+H)^+$.

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Example 2.8:

In analogy with example 1.1) with 3-chlorophenyl boronic acid and 7-bromo-2-methyl-4-piperidin-1-yl-quinazoline (Example 4.1) there is obtained 7-(3-chloro-phenyl)-2-methyl-4-piperidin-1-yl-quinazoline as a light-yellow solid. MS (ISP): 338.2$(M+H)^+$.

Example 2.9:

In analogy with example 1.1) with 3-trifluoromethylphenylboronic acid and 4-azepan-1-yl-7-bromo-2-methyl-quinazoline (Example 4.3) there is obtained 4-azepan-1-yl-2-methyl-7-(3-trifluoromethyl-phenyl)-quinazoline as an off-white amorphous solid. MS (ISP): 386.3$(M+H)^+$.

Example 3.1:

Preparation of 7-iodo-2-methyl-4-pyrrolidin-1-yl-quinoline:

A suspension of 2g of 4-chloro-7-iodo-2-methyl-quinoline (European patent application EP 0497371, CA 143946-47-8) in 20 ml absolute ethanol is treated successively with 1.09 ml pyrrolidine, 0.2 ml pyridine and 50 mg potassium iodide under argon. The resulting mixture is refluxed for 24 h. The solvent is then distilled off. The residue is taken up in 50 ml water and basified to pH 12 with a 2N solution of sodium hydroxyde. The solid is filtered upon precipitation and washed with 20 ml of water and 20 ml of diethylether. The final product is dried under vacuum yielding 1.95 g (87%) of 7-iodo-2-methyl-4-pyrrolidin-1-yl-quinoline as an off-white solid. Mp: 99-102°C. MS (EI): peaks at m/e: 338(M+, 100%), 296 (5%), 183(9%).

Example 3.2:

In analogy with Example 3.1) with 4-chloro-7-iodo-2-methyl-quinoline and piperidine there is obtained 7-iodo-2-methyl-4-piperidin-1-yl-quinoline as a light-yellowish solid. Mp. 124-126°C. MS (EI): peaks at m/e: 352(M+, 100%), 296 (4%), 269(5%).

Example 3.3:

In analogy with Example 3.1) with 4-chloro-7-iodo-2-methyl-quinoline and diethylamine in an autoclave for 120h at 150°C there is obtained diethyl-(7-iodo-2-methyl-quinolin-4-yl)-amine as a reddish oil. MS (EI): peaks at m/e: 339(M+, 100%), 325 (73%), 198(43%).

Example 3.4:

In analogy with Example 3.1) with 4-chloro-7-iodo-2-methyl-quinoline and morpholine there is obtained 7-iodo-2-methyl-4-morpholin-4-yl-quinoline as an off-white solid. Mp. 103-105°C. MS (EI): peaks at m/e: 354(M+, 100%), 296 (73%), 169(13%).

Example 3.5:

In analogy with Example 3.1) with 4-chloro-7-iodo-2-methyl-quinoline and N-methylpiperazine there is obtained 7-iodo-2-methyl-4-(4-methyl-piperazin-1-yl)-quinoline as a light-brownish solid. Mp. 92-94°C. MS (EI): peaks at m/e: 367(M+, 100%), 352 (38%), 310(11%).

Example 3.6:

In analogy with Example 3.1) with 4-chloro-7-iodo-2-methyl-quinoline and tetrahydroisoquinoline there is obtained 4-(3,4-dihydro-1H-isoquinolin-2-yl)-7-iodo-2-methyl-quinoline hydrochloride as a beige solid. Mp. > 230°C. MS (ISP): 401.3$(M+H)^+$.

Example 3.7:

In analogy with Example 3.1) with 4-chloro-5-iodo-2-methyl-quinoline (Example 5.2) and piperidine there is obtained 5-iodo-2-methyl-4-piperidin-1-yl-quinoline as an orange oil. MS (ISP): 353.2$(M+H)^+$.

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Example 3.8:

In analogy to Example 3.1) with 4-chloro-5-iodo-2-methyl-quinoline and pyrrolidine there is obtained 5-iodo-2-methyl-4-pyrrolidin-1-yl-quinoline as a light-yellow solid. Mp. 97-99°C. MS (ISP): 339.1$(M+H)^+$.

Example 3.9:

In analogy to Example 3.1) with 4-chloro-5-iodo-2-methyl-quinoline and morpholine there is obtained 5-iodo-2-methyl-4-morpholin-4-yl-quinoline as a yellow solid. Mp. 144-145°C. MS (ISP): 355.1$(M+H)^+$.

Example 3.10:

In analogy with Example 3.1) with 4-chloro-7-iodo-2-methyl-quinoline and azepine there is obtained 4-azepan-1-yl-7-iodo-2-methyl-quinoline as a beige solid. Mp. > 90-93°C. MS (ISP): 367.1$(M+H)^+$.

Example 3.11:

In analogy with Example 3.1) with 6-bromo-4-chloro-2-methyl-quinoline (Example 5.3) and pyrrolidine there is obtained 6-bromo-2-methyl-4-pyrrolidin-1-yl-quinoline as a beige solid. MS (ISP): 291.2$(M+H)^+$.

Example 3.12:

In analogy with Example 3.1) with 7-bromo-4-chloro-quinoline (J. Amer. Chem. Soc. 1946, 68, 113-116)and pyrrolidine there is obtained 7-bromo -4-pyrrolidin-1-yl-quinoline as a beige solid. MS (ISP): 277.2$(M+H)^+$.

Example 4.1:

Preparation of 7-bromo-2-methyl-4-piperidin-1-yl-quinazoline:

In analogy to Example 3.1) with 7-bromo-4-chloro-2-methyl-quinazoline (Example 5.1) and piperidine there is obtained 7-bromo-2-methyl-4-piperidin-1-yl-quinazoline as an amorphous yellow solid. MS (ISP): 306.2$(M+H)^+$.

Example 4.2:

In analogy to Example 3.1) with 7-bromo-4-chloro-2-methyl-quinazoline (Example 5.1) and pyrrolidine there is obtained 7-bromo-2-methyl-4-pyrrolidin-1-yl-quinazoline as a yellow solid. Mp. 120-122°C. MS (ISP): 292.2$(M+H)^+$.

Example 4.3:

In analogy to Example 3.1) with 7-bromo-4-chloro-2-methyl-quinazoline (Example 5.1) and azepine there is obtained 4-azepan-1-yl-7-bromo-2-methyl-quinazoline as an orange oil. MS (ISP): 320.3$(M+H)^+$.

Example 4.4:

In analogy to Example 3.1) with 7-bromo-4-chloro-2-methyl-quinazoline (Example 5.1) and azetidine there is obtained 4-azetidin-1-yl-7-bromo-2-methyl-quinazoline as a light-brown solid. Mp. 129-131°C. MS (ISP): 278.1$(M+H)^+$.

Example 4.5:

In analogy to Example 3.1) with 7-bromo-4-chloro-2-methyl-quinazoline (Example 5.1) and dimethylamine there is obtained (7-bromo-2-methyl-quinazolin-4-yl)-dimethyl-amine as a brown solid. Mp. 55-57°C. MS (ISP): 266.2$(M+H)^+$.

Example 4.6:

In analogy to Example 3.1) with 7-bromo-4-chloro-2-methyl-quinazoline (Example 5.1) and n-butylamine there is obtained (7-bromo-2-methyl-quinazolin-4-yl)-butyl-amine as a beige solid. Mp. 133-135°C. MS (ISP): 294.2$(M+H)^+$.

Example 5.1:

Preparation of 7-bromo-4-chloro-2-methyl-quinazoline:

A suspension of 0.45 g 7-bromo-2-methyl-3H-quinazolin-4-one in 0.48 ml N,N-dimethylaniline is treated with 1.41ml phosphourous oxychloride and heated at 60°C for 2h. The reaction mixture is evaporated in vacuo and the residue is taken up with 20 ml water, neutralized with 10 ml saturated aqueous sodium bicarbonate and extracted with 25 ml dichloromethane twice. The organic layer is washed with 25 ml water, 25 ml brine, dried over magnesium sulfate and evaporated in vacuo. The residue is purified by chromatography on silica gel with Heptane/ethylacetate 2:1. 0.288g (59%) of 7-bromo-4-chloro-2-methyl-quinazoline are obtained as an orange solid. Mp. >82°C (dec). MS (EI): peaks at m/e: 258(M+, 37%), 221 (100%), 179(9%).

Example 5.2:

Preparation of 4-chloro-5-iodo-2-methyl-quinoline

25 g of crude 3-(3-Iodo-phenylamino)-but-2-enoic acid ethyl ester (Example 7.1) is added rapidly to 25 ml boiling Dowtherm A, keeping the internal temperature above 250°C. After 1.5h of reaction time, the mixture is cooled at room temperature. The solid which separates is filtered, washed with 50 ml dichloromethane and dried in vacuo to obtain 17.27g (83.6%) of a mixture of 7-iodo-2-methyl-quinolin-4-ol and 5-iodo-2-methyl-quinolin-4-ol.

To 17.27 g of the above product is added 20 ml phosphorous oxychloride. The resulting suspension is stirred at room temperature for 2 h. The crystalline product is triturated with 50ml dry diethylether and filtered. The cake is suspended in 50 ml ice water and concentrated ammonium hydroxide is added until the resulting suspension is permanently basic. The product is filtered, washed with 50 ml water and dried in vacuo. Purification of the crude product by chromatography on silica gel with Heptane/ethylacetate 2:1 gives 7.1g (41%) of 4-chloro-7-iodo-2-methyl-quinoline and 4.26g (23%) of 4-chloro-5-iodo-2-methyl-quinoline as a beige solid. Mp. 98-100°C. MS (EI): peaks at m/e: 303 (M+, 100%), 176 (100%), 140(21%).

Example 5.3:

In analogy with Example 5.1) with 6-bromo-4-hydroxy-2-methyl-quinoline (Synthesis, 1987, 482-483) there is obtained 6-Bromo-4-chloro-2-methyl-quinoline as a light-purple solid. MS (EI): peaks at m/e: 256(M+, 100%), 220 (13%), 141(20%).

Example 6.1:

Preparation of 7-bromo-2-methyl-3H-quinazolin-4-one:

To a solution of 0.81g 4-bromoanthranilic acid (J. Org. Chem. 1997, 62, 1240-1256), 39 mg 4-(dimethylamino)pyridine and 2.09 ml triethylamine in dry dimethylformamide is added dropwise 0.69 ml acetylchloride at 3°C for 20 min. in an ice-water bath under argon. The reaction mixture is then heated at 90°C for 3 h. and 1.08 g ammonium carbonate is added portionwise over 10 min., and the mixture is stirred at the same temperature for 1 h. After cooling, the mixture is poured onto 20 ml water and the precipitate is filtered, washed with water and dried in vacuo to give 0.46 g (51%) of crude 7-Bromo-2-methyl-3H-quinazolin-4-one as a light-brown solid. Mp. >191°C (dec.). MS (EI): peaks at m/e: 240(M+, 100%), 223 (14%), 197(18%).

Example 7.1:

Preparation of 3-(3-iodo-phenylamino)-but-2-enoic acid ethyl ester:

A mixture of 47.79 g 3-iodoaniline, 27.7 ml ethyl acetoacetate and 0.13 ml 37% hydrochlorid acid in 65 ml benzene is boiled under a reflux condenser fitted with a water separator. After 4 h. 4 ml of water have been collected. The solvent is removed at reduced pressure and the residual oil dried in vacuo. 3-(3-iodo-phenylamino)-but-2-enoic acid ethyl ester is obtained as a light brown oil. MS (ISP): 332.1 $(M+H)^+$.

Example 8.1

Preparation of 7-(4-Methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinazoline; compound with formic acid:

To a solution of 44 mg (0.15 mmol) 7-Bromo-2-methyl-4-pyrrolidin-1-yl-quinazoline in 1.2 ml dioxane / dimethoxyethane 1:1 was added 57 mg (0.375 mmol) 4-methoxy-phenyl-

boronic acid in 0.4 ml ethanol, 7 mg (0.007 mmol) Dichloro[1,1'-Bis(diphenylphosphino)-ferrocene]-palladium (II) dichloromethan adduct, and 0.6 ml 2 M Na_2CO_3aq. and the mixture was heated to 85°C for 12 h. After filtration, the mixture was purified by reversed phase column chromatography eluting with an acetonitrile / water (formic acid) gradient yielding 17 mg (35%) of the title compound. MS m/e (%): 320.4 ($M+H^+$, 100)

According to example 8.1 further quinazoline derivatives have been synthesised. The results are compiled in the following list comprising example 8.2 to example 8.15.

The isolated formiates 8.1-8.15 can each be transferred to the respective parent compound by treatment with base.

The examples 8.2-8.15 have each been synthesised from 7-Bromo-2-methyl-4-pyrrolidin-1-yl-quinazoline and the respective boronic acid or the 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-derivative thereof comprised in the following table:

Ex.	Boronic acid or the 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-derivative thereof	Product Name	MH^+ found
8.2	4,4,5,5-Tetramethyl-2-thiophen-3-yl-[1,3,2]dioxaborolane (Lit.: WO 0027853A1)	2-Methyl-4-pyrrolidin-1-yl-7-thiophen-3-yl-quinazoline; compound with formic acid	296.4
8.3	[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-carbamic acid tert-butyl ester (Lit.: WO 0119829A2, CSIRO, Molecular Science, Clayton South VIC 3169, Australia)	[4-(2-Methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenyl]-carbamic acid tert-butyl ester; compound with formic acid	405.5

8.4	3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile (Lit.: WO 9845265A1)	3-(2-Methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-benzonitrile; compound with formic acid	315.4
8.5	3,5-Dichloro-benzeneboronic acid (commercially available)	7-(3,5-Dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinazoline; compound with formic acid	359.3
8.6	3-Acetylphenylboronic acid (commercially available)	1-[3-(2-Methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenyl]-ethanone; compound with formic acid	332.4
8.7	4-Trifluoromethylphenyl-boronic acid (commercially available)	2-Methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethyl-phenyl)-quinazoline; compound with formic acid	358.4
8.8	Thiophene-2-boronic acid (commercially available)	2-Methyl-4-pyrrolidin-1-yl-7-thiophen-2-yl-quinazoline; compound with formic acid	296.4

8.9	5-Acety-2-thiopheneboronic acid (commercially available)	1-[5-(2-Methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-thiophen-2-yl]-ethanone; compound with formic acid	338.4
8.10	5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole (Lit.: WO 0027853A1)	7-(1H-Indol-5-yl)-2-methyl-4-pyrrolidin-1-yl-quinazoline	329.4
8.11	N-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetamide (Lit.: WO 0027853A1)	N-[2-Methyl-4-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenyl]-acetamide; compound with formic acid	361.5
8.12	3-Nitrophenylboronic acid (commercially available)	Formic acid; 2-methyl-7-(3-nitro-phenyl)-4-pyrrolidin-1-yl-quinazoline	335.4
8.13	3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (WO 9831688A1)	3-(2-Methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenylamine; compound with formic acid	305.4
8.14	3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (commercially available)	3-(2-Methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenol; compound with formic acid	306.4

8.15	(3-Trifluoromethoxy)-benzeneboronic acid (commercially available)	2-Methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethoxy-phenyl)-quinazoline; compound with formic acid	374.4

Example 9.1

2-Methyl-7-phenyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid:

To a solution of 43 mg (0.13 mmol) 7-Iodo-2-methyl-4-pyrrolidin-1-yl-quinoline in 1.2 ml dioxane / dimethoxyethane 1:1 was added 39.6 mg (0.325 mmol) phenyl-boronic acid, 6 mg (0.007 mmol) Dichloro[1,1'-Bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethan adduct, and 0.55 ml 2M Na_2CO_3aq. and the mixture was heated to 85°C for 12 h. After filtration the mixture was purified by reversed phase column chromatography eluting with an acetonitrile/water (formic acid) gradient yielding 25 mg (57 %) of the title compound. MS m/e (%): 289.4 (MH^+, 100)

According to example 9.1 further quinoline derivatives have been synthesised. The results are compiled in the following table No 2 comprising example 9.2 to example 9.39.

The isolated formiates 9.1-9.39 can each be transferred to the respective parent compound by treatment with base.

The examples 9.2-9.39 have each been synthesised from 7-Iodo-2-methyl-4-pyrrolidin-1-yl-quinoline and the respective boronic acid or the 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-derivative thereof comprised in the following starting material list.

Ex.	Boronic acid or the 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-derivative thereof	Product Name	MH^+ found
9.2	4-Ethylphenylboronic acid (commercially available)	7-(4-Ethyl-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	317.4
9.3	3,4-Dimethoxyphenylboronic acid (commercially available)	7-(3,4-Dimethoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	349.4
9.4	2,6-Difluorophenylboronic acid (commercially available)	7-(2,6-Difluoro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	325.4
9.5	2,4-Dimethoxyphenylboronic acid (commercially available)	7-(2,4-Dimethoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	349.4
9.6	4-Trifluoromethylboronic acid (commercially available)	2-Methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethyl-phenyl)-quinoline; compound with formic acid	357.4

9.7	4-(Methylthio)-phenylboronic acid (commercially available)	2-Methyl-7-(4-methylsulfanyl-phenyl)-4-pyrrolidin-1-yl-quinoline; compound with formic acid	335.5
9.8	2-Methoxyphenylboronic acid (commercially available)	7-(2-Methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	319.4
9.9	3-Ethoxyphenylboronic acid (commercially available)	7-(3-Ethoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	333.4
9.10	3-Acetamidophenylboronic acid (commercially available)	N-[3-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-acetamide; compound with formic acid	346.4
9.11	4-Trifluoromethoxyboronic acid (commercially available)	2-Methyl-4-pyrrolidin-1-yl-7-(4-trifluoromethoxy-phenyl)-quinoline; compound with formic acid	373.4

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9.12	(3,4-Methylenedioxyphenyl)boronic acid (commercially available)	7-Benzo[1,3]dioxol-5-yl-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	333.4
9.13	Benzo[B]furan-2-boronic acid (commercially available)	7-Benzofuran-2-yl-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	329.4
9.14	Benzo[B]thiophene-2-boronic acid (commercially available)	7-Benzo[b]thiophen-2-yl-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	345.5
9.15	3-Chloro-4-fluorophenylboronic acid (commercially available)	7-(3-Chloro-4-fluoro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	341.8
9.16	5-Acetyl-thiopheneboronic acid (commercially available)	1-[5-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-thiophen-2-yl]-ethanone; compound with formic acid	337.5

9.17	3,4-Dichlorophenylboronic acid (commercially available)	7-(3,4-Dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	358.3
9.18	2-Fluorophenylboronic acid (commercially available)	7-(2-Fluoro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	307.4
9.19	1-Naphtaleneboronic acid (commercially available)	2-Methyl-7-naphthalen-1-yl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	339.5
9.20	2-Chlorophenylboronic acid (commercially available)	7-(2-Chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	323.8
9.21	4-Vinylphenylboronic acid (commercially available)	2-Methyl-4-pyrrolidin-1-yl-7-(4-vinyl-phenyl)-quinoline; compound with formic acid	315.4

9.22	3,5-Bis(trifluoromethyl)phenylboronic acid (commercially available)	7-(3,5-Bis-trifluoromethyl-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	425.4
9.23	3-Methoxyphenylboronic acid (commercially available)	7-(3-Methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	319.4
9.24	3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid ethyl ester (Lit.: WO 0027853A1)	3-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-benzoic acid ethyl ester; compound with formic acid	361.5
9.25	4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid ethyl ester (commercially available)	4-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-benzoic acid ethyl ester; compound with formic acid	361.5

9.26	2-Methoxy-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (Lit.: WO 0027853A1)	2-Methoxy-4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol; compound with formic acid	335.4
9.27	N-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetamide (commercially available)	N-[4-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-acetamide; compound with formic acid	346.4
9.28	Dimethyl-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amine (Lit.: J. Org. Chem. 2000, 65, 164-168)	Dimethyl-[4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-amine; compound with formic acid	332.5
9.29	3,5-Dichlorophenylboronic acid (commercially available)	7-(3,5-Dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	358.3
9.30	2-Naphtaleneboronic acid (commercially available)	2-Methyl-7-naphthalen-2-yl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	339.5

9.31	N-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Lit.: WO 9845265A1)	N-Methyl-4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-benzamide; compound with formic acid	346.4
9.32	3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (commercially available)	3-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol; compound with formic acid	305.4
9.33	2-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (Lit.: WO 0027853A1)	2-Methoxy-5-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol; compound with formic acid	335.4
9.34	2,6-Dimethoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (Lit.: WO 9845265A1)	7-(2,6-Dimethoxy-pyridin-3-yl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	350.4

9.35	2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (Lit.: WO 0027853A1)	2-(2-Methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol; compound with formic acid	305.4
9.36	4,4,5,5-Tetramethyl-2-(4-phenoxy-phenyl)-[1,3,2]dioxaborolane (Lit.: WO 0027853A1)	2-Methyl-7-(4-phenoxy-phenyl)-4-pyrrolidin-1-yl-quinoline; compound with formic acid	381.5
9.37	2-(2,6-Dichloro-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (Lit.: J. Chromatogr. 1979, 186, 307-316)	7-(2,6-Dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline; compound with formic acid	358.3
9.38	3-Trifluoromethoxyboronic acid (commercially available)	2-Methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethoxy-phenyl)-quinoline; compound with formic acid	373.4
9.39	2-Trifluoromethoxyboronic acid (commercially available)	2-Methyl-4-pyrrolidin-1-yl-7-(2-trifluoromethoxy-phenyl)-quinoline; compound with formic acid	373.4

Example A

A compound of formula I can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	Per tablet
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	20 mg
	425 mg

Example B

A compound of formula I can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	Per capsule
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg
	220.0 mg

EXAMPLE C

Tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet
Compound of formula I	10.0 - 100.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

EXAMPLE D

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula I	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

EXAMPLE E

Injection solutions can have the following composition:

Compound of formula I	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Water for injection solutions	ad 1.0 ml

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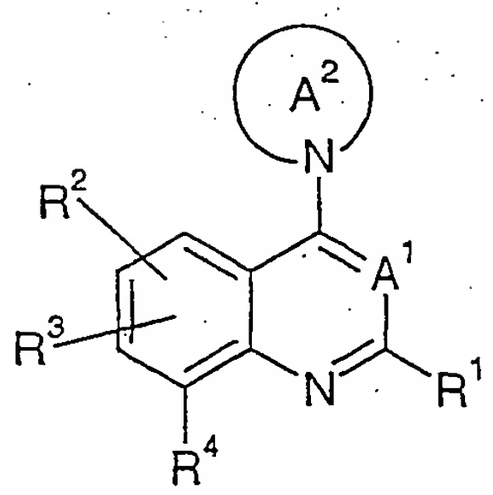
Claims

1. Compounds of formula I



I

wherein

R^1 is alkyl, cycloalkyl, aralkyl or trifluoroalkyl;

R^2 is hydrogen, alkyl, alkoxy, hydroxy, halogen, trifluoroalkyl, difluoroalkoxy or trifluoroalkoxy;

R^3 is aryl or heteroaryl;

R^4 is hydrogen;

R^5 is hydrogen, alkyl or aralkyl;

R^6 and R^7 are each independently hydrogen or alkyl;

A^1 is CH or N;

A^2 is a 4- to 10- membered heterocylic ring optionally substituted with alkyl, hydroxy, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxyalkoxy, -$COOR^5$ or –$CONR^6R^7$;

and pharmaceutically usable salts, solvates and esters thereof.

2. Compounds according to claim 1, wherein R^2 is hydrogen.

3. Compounds according to claim 1 or 2, wherein R^1 is alkyl.

4. Compounds according to claim 3, wherein R^1 is methyl.

5. Compounds according to any one of claims 1 to 4, wherein R^3 is attached at the 7-position of the quinoline or quinazoline ring.

6. Compounds according to any one of claims 1 to 5, wherein A^1 is CH.

7. Compounds according to any one of claims 1 to 5, wherein A^1 is N.

8. Compounds according to any one of claims 1 to 7, wherein R^3 is unsubstituted phenyl, thiophenyl, pyridinyl, pyrimidinyl, 1H-indolyl, benzofuryl, benzothiophenyl or naphthyl or R^3 is phenyl, thiophenyl, pyridinyl, pyrimidinyl, 1H-indolyl, benzofuryl, benzothiophenyl or naphthyl, substituted with one to three substituents each independently selected from halogen, trifluoromethyl, amino, alkoxy, methylendioxy, alkylcarbonyl, cyano, alkyl, nitro, hydroxy, trifluoromethoxy, alkylsulfanyl, alkenyl, alkoxycarbonyl, aryloxy, alkoxycarbonylamino, alkylcarbonylamino and aminocarbonyl.

9. Compounds according to claim 8, wherein R^3 is unsubstituted thiophenyl, pyridinyl or naphthyl or R^3 is phenyl or thiophenyl substituted with one or two substituents each independently selected from halogen, trifluoromethyl, alkoxy, alkylcarbonyl, cyano and hydroxy.

10. Compounds according to any one of claims 1 to 9, wherein A^2 is a 4- to 10-membered heterocylic ring optionally substituted with alkyl.

11. Compounds according to claim 10, wherein A^2 is a pyrrolidine, piperidine, morpholine, piperazine, 3,4-dihydro-1H-isoquinoline or azepane ring, wherein these rings are optionally substituted with alkyl.

12. Compounds in accordance with any one of claims 1 to 11, selected from

7-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinoline;

1-[4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenyl]-ethanone;

7-(4-methoxy-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-thiophen-2-yl-quinoline;

2-methyl-7-pyridin-3-yl-4-pyrrolidin-1-yl-quinoline;

2-methyl-4-piperidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinoline;

5-(3-chloro-phenyl)-2-methyl-4-piperidin-1-yl-quinoline;

4-azepan-1-yl-2-methyl-7-(3-trifluoromethyl-phenyl)-quinoline;

2-methyl-4-pyrrolidin-1-yl-7-(3-trifluoromethyl-phenyl)-quinazoline;

7-(3-chloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinazoline;

4-azepan-1-yl-2-methyl-7-(3-trifluoromethyl-phenyl)-quinazoline;

3-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-benzonitrile;

1-[3-(2-methyl-4-pyrrolidin-1-yl-quinazolin-7-yl)-phenyl]-ethanone;

7-(3-chloro-4-fluoro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

1-[5-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-thiophen-2-yl]-ethanone;

7-(3,4-dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline;

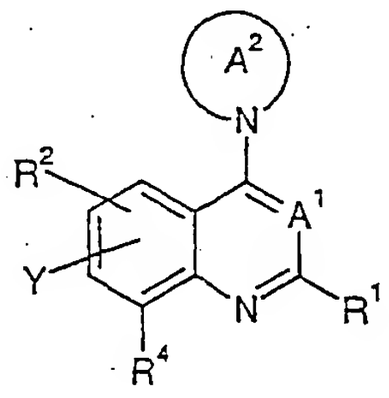
2-methoxy-4-(2-methyl-4-pyrrolidin-1-yl-quinolin-7-yl)-phenol;

7-(3,5-dichloro-phenyl)-2-methyl-4-pyrrolidin-1-yl-quinoline and

2-methyl-7-naphthalen-2-yl-4-pyrrolidin-1-yl-quinoline.

13. A process for the preparation of a compound according to any one of claims 1 to 12, comprising one of the following reactions:

a) the reaction of a compound of formula



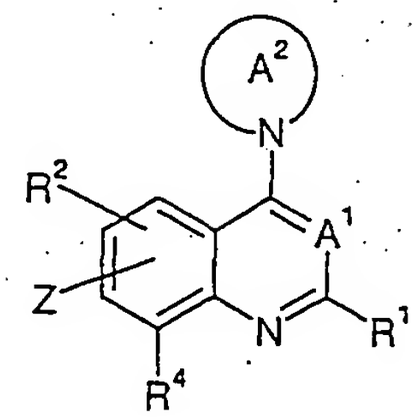
IIIa

in the presence of a compound of formula

R^3—Z IIa

or

b) the reaction of a compound of formula



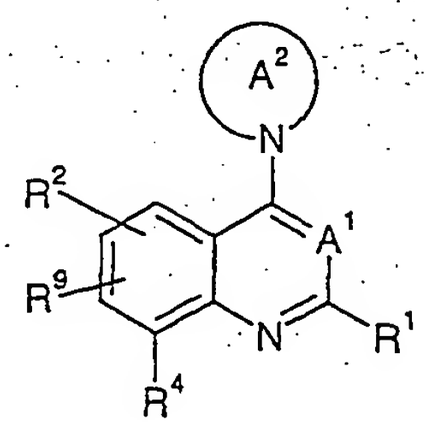
IIIb

in the presence of a compound of formula

R^3—Y IIb ,

wherein R^1, R^2, R^3, R^4, A^1 and A^2 are defined as in any one of claims 1 to 11 and Y and Z are substituents which can be used in transition metal catalysed cross coupling reactions.

14. Compounds of the formula X



X

wherein R^1, R^2, R^4, A^1 and A^2 are defined as in any of claims 1 to 11 and, wherein R^9 is iodine, bromine, chlorine, methylsulfonyloxy, trifluoromethylsulfonyloxy, phenylsulfonyloxy or p-tosylsulfonyloxy.

15. Compounds in accordance with any one of claims 1 to 12 for use as therapeutically active substances.

16. Compounds in accordance with any one of claims 1 to 12 for the production of medicaments for the prophylaxis and therapy of illnesses which are caused by disorders associated with the NPY receptor.

17. A pharmaceutical composition containing a compound in accordance with any one of claims 1 to 12 and a therapeutically inert carrier.

18. The use of compounds in accordance with any one of claims 1 to 12 for the production of medicaments for the treatment and prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure, eating disorders and obesity.

19. Compounds in accordance with any one of claims 1 to 12, when manufactured according to claim 13.

20. A method for the treatment and prophylaxis of arthritis, cardiovascular diseases, diabetes, renal failure, eating disorders and obesity, which method comprises administering an effective amount of a compound in accordance with any one of claims 1 to 12.

21. A method of treatment of obesity in a human in need of such treatment which comprises administration to the human a therapeutically effective amount of a compound according to any one of claims 1 to 12 and a therapeutically effective amount of a lipase inhibitor.

22. The method according to claim 21, wherein the lipase inhibitor is orlistat.

23. The method according to claims 21 and 22 for the simultaneous, separate or sequential administration.

24. The use of a compound according to any one of claims 1 to 12 in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor.

25. The use according to claim 24, wherein the lipase inhibitor is orlistat.

26. The pharmaceutical composition according to claim 17 comprising further a therapeutically effective amount of a lipase inhibitor.

27. The pharmaceutical composition according to claim 26, wherein the lipase inhibitor is orlistat.

28. The invention as hereinbefore described.

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(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basle (CH).

(72) Inventors: BREU, Volker; 9a Leonhard-Mueller-Strasse, 79418 Schliengen (DE). DAUTZENBERG, Frank; 75 Vogesenstrasse, 79379 Muelheim (DE). GUERRY, Philippe; In den Holeematten 2, CH-4102 Binningen (CH). NETTEKOVEN, Matthias, Heinrich; Bandweg 10, 79639 Grenzach-Wyhlen (DE). PFLIEGER, Philippe; 1, rue du Vignoble, F-68130 Schwoben (FR).

(74) Agent: WITTE, Hubert; 124 Grenzacharstrasse, CH-4070 Basle (CH).

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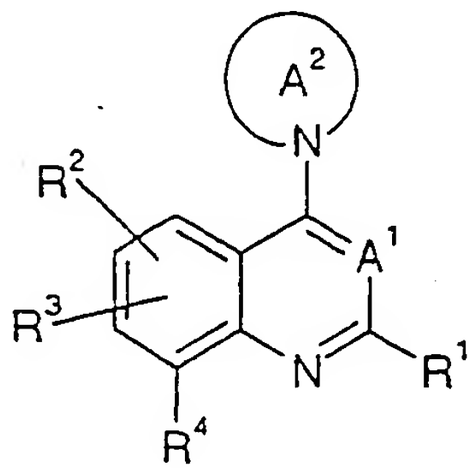
(54) Title: QUINOLINE AND QUINAZOLINE DERIVATIVES AS LIGANDS FOR THE NEUROPEPTIDE Y RECEPTOR



(I)

(57) Abstract: Compounds of formula (I) as well as pharmaceutically usable salts, solvates and esters thereof, wherein R^1, R^2, R^3, R^4, A^1 and A^2 have the significance given in claim 1, can be used in the form of pharmaceutical preparations for the treatment or prevention of arthritis, cardiovascular diseases, diabetes, renal failure, eating disorders and obesity.

INT RNATIONAL SEARCH REPORT

Inter onal Application No
PCT/EP 01/10014

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/42 C07D409/04 C07D401/04 C07D239/84 A61P3/00
A61K31/517 A61K31/4706

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2002	01/03/2002

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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NSDOCID: <WO_ 0220488A3_I >